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247 HOXC8

11121 SMAD?

S1 7 HOXC8 AND SMAD?

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Set	Items	Description
S1	7	HOXC8 AND SMAD?
S2	7	RD (unique items)

>>>KWIC option is not available in file(s): 41, 77, 399

**2/3,K/1 (Item 1 from file: 399)**  
 DIALOG(R)File 399:CA SEARCH(R)  
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**135353612 CA: 135(25)353612u JOURNAL**  
**Transcriptional mechanisms of bone morphogenetic protein-induced osteoprotegrin gene expression**  
 AUTHOR(S): Wan, Mei; Shi, Xingming; Feng, Xu; Cao, Xu  
 LOCATION: Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA  
 JOURNAL: J. Biol. Chem. DATE: 2001 VOLUME: 276 NUMBER: 13 PAGES: 10119-10125 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

**2/3,K/2 (Item 2 from file: 399)**  
 DIALOG(R)File 399:CA SEARCH(R)  
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**135190556 CA: 135(14)190556n JOURNAL**  
**Smad interactors in bone morphogenetic protein signaling**  
 AUTHOR(S): Yang, Xiangli; Cao, Xu  
 LOCATION: Department of Pathology, University of Alabama, Birmingham, AL, USA  
 JOURNAL: Methods Mol. Biol. (Totowa, NJ, U. S.) DATE: 2001 VOLUME: 177 NUMBER: Two-Hybrid Systems PAGES: 163-178 CODEN: MMBIED ISSN: 1064-3745 LANGUAGE: English PUBLISHER: Humana Press Inc.

**2/3,K/3 (Item 3 from file: 399)**  
 DIALOG(R)File 399:CA SEARCH(R)  
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**134364569 CA: 134(26)364569r DISSERTATION**  
**Bone morphogenetic proteins induce gene transcription and osteoblastic differentiation through the interaction between Smad1 and Hoxc-8**  
 AUTHOR(S): Yang, Xiangli  
 LOCATION: University of Alabama at Birmingham, USA  
 DATE: 2000 PAGES: 204 pp. CODEN: DABBBA LANGUAGE: English CITATION: Diss. Abstr. Int., B 2000, 61(3), 1234 AVAIL: UMI, Order No. DA9964660

2/3,K/4 (Item 4 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

134158510 CA: 134(12)158510m PATENT  
**The interaction of Smad6 with Hox proteins and BMP signalling and uses thereof in regulation of bone formation**  
INVENTOR(AUTHOR): Cao, Xu; Shi, Xingming; Bai, Shuting  
LOCATION: USA  
ASSIGNEE: Uab Research Foundation  
PATENT: PCT International ; WO 0111013 A2 DATE: 20010215  
APPLICATION: WO 2000US40563 (20000803) \*US PV147161 (19990804)  
PAGES: 34 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-000/A  
DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM ; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

2/3,K/5 (Item 5 from file: 399)  
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132178572 CA: 132(14)178572v JOURNAL  
**Smad1 domains interacting with Hoxc-8 induce osteoblast differentiation**  
AUTHOR(S): Yang, Xiangli; Ji, Xiaohui; Shi, Xingming; Cao, Xu  
LOCATION: Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA  
JOURNAL: J. Biol. Chem. DATE: 2000 VOLUME: 275 NUMBER: 2 PAGES: 1065-1072 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

2/3,K/6 (Item 6 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
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131098451 CA: 131(8)98451u JOURNAL  
**Smad1 interacts with homeobox DNA-binding proteins in bone morphogenetic protein signaling**  
AUTHOR(S): Shi, Xingming; Yang, Xiangli; Chen, Di; Chang, Zhijie; Cao, Xu  
LOCATION: Department of Pathology, University of Alabama School of Medicine, Birmingham, AL, 35294, USA  
JOURNAL: J. Biol. Chem. DATE: 1999 VOLUME: 274 NUMBER: 19 PAGES: 13711-13717 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

2/3,K/7 (Item 1 from file: 266)  
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00319803  
IDENTIFYING NO.: 1R01DK57501-01A1 AGENCY CODE: CRISP  
**MECHANISM OF \*SMAD1\* MEDIATED OSTEOBLAST DIFFERENTIATION**  
PRINCIPAL INVESTIGATOR: CAO, XU  
ADDRESS: UNIV OF ALABAMA, BIRMINGHAM 1670 UNIVERSITY BLVD, VH G001 BIRMINGHAM, AL 35294-0019  
PERFORMING ORG.: UNIVERSITY OF ALABAMA AT BIRMINGHAM, BIRMINGHAM, ALABAMA  
SPONSORING ORG.: NAT INST OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES  
FY : 2001

#### MECHANISM OF \*SMAD1\* MEDIATED OSTEOBLAST DIFFERENTIATION

...SUMMARY: superfamily, are potent growth factors in inducing osteoblast differentiation and stimulating bone formation. Signaling in TGF-beta superfamily is mediated by direct phosphorylation of \*Smad\* proteins. \*Smad2\* and \*Smad3\* are phosphorylated by TGF-beta and activin receptors, whereas phosphorylation of \*Smad1\* is specifically induced by bone morphogenetic proteins. Upon phosphorylation these \*Smad\* proteins interact with a common partner, \*Smad4\*, and translocate into the nucleus where the complex recruits DNA binding protein(s) to activate specific gene transcription. However, the DNA binding protein(s) involved in BMP signaling has not been identified. We have demonstrated that BMPs induce the interaction of \*Smad1\* with Hoxc-8, a member of the homeodomain transcription factor family. The interaction of \*Smad1\* with Hoxc-8 inhibits the binding of Hoxc-8 to its DNA binding site. Hoxc-8 functions as a transcription repressor. A hox binding...

... osteopontin gene transcription is mediated through this Hox binding site. We hypothesize that BMP-2/4 induces osteoblast cell differentiation mediated by the \*Smad1\* interaction with Hoxc-8. The specific aims proposed are to: 1) characterize the specificity of the interaction between \*Smad1\* and Hox proteins in BMP2/4 signaling; 2) map domains that are responsible for the interaction between \*Smad1\* and \*Hoxc8\*. The effect of mapped \*Smad1\* interaction domains on gene transcription will also be assessed in luciferase reporter transfection studies. 3) Characterize the effects of the interaction between \*Smad1\* and Hoxc-8 on osteoblast differentiation in human primary stromal cells. Further characterization of the interaction between \*Smad1\* and Hoxc-8 will help us to understand the mechanism of BMP signaling and may yield a potential drug target to stimulate bone formation...

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Set	Items	Description
S1	7	SMAD6 (5N) HOX
S2	2	RD (unique items)
S3	585	SMAD6
S4	17	S3 (S) HOX?
S5	6	RD (unique items)
S6	6	RD (unique items)

et	Items	Description
S1	7	SMAD6 (5N) HOX
S2	2	RD (unique items)
S3	585	SMAD6
S4	17	S3 (S) HOX?
S5	6	RD (unique items)
S6	6	RD (unique items)

>>>KWIC option is not available in file(s): 41, 77, 399

**6/3,K/1 (Item 1 from file: 5)**  
 DIALOG(R)File 5:Biosis Previews(R)  
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13556490 BIOSIS NO.: 200200185311

**A nuclear antagonistic mechanism of inhibitory Smads in transforming growth factor-beta signaling.**

AUTHOR: Bai Shuting; Cao Xu(a)  
 AUTHOR ADDRESS: (a)Dept. of Pathology, University of Alabama at Birmingham  
 School of Medicine, 1670 University Blvd., VH G002, Birmingham, AL,  
 35294-0019\*\*USA E-Mail: cao@path.uab.edu  
 JOURNAL: Journal of Biological Chemistry 277 (6):p4176-4182 February 8,  
 2002  
 MEDIUM: print  
 ISSN: 0021-9258  
 DOCUMENT TYPE: Article  
 RECORD TYPE: Abstract  
 LANGUAGE: English

ABSTRACT: Inhibitory Smads (I-Smads), including \*Smad6\* and Smad7, were initially characterized as cytoplasmic antagonists in the transforming growth factor-beta signaling pathway. However, I-Smads are also localized in the nucleus. Previously, we have shown that \*Smad6\* can function as a transcriptional co-repressor. In this study, we found both \*Smad6\* and Smad7 interact with histone deacetylases (HDACs). Acetylation state of core histones plays a critical role in gene transcription regulation. An HDAC inhibitor, trichostatin A, released \*Smad6\*-mediated transcription repression. Moreover, class I HDACs (HDAC-1 and -3), not class II HDACs (HDAC-4, -5, and -6), were co-immunoprecipitated with \*Smad6\*. Endogenous HDAC-1 was also shown to interact with both \*Smad6\* and \*Hoxc\*-8. Mapping of the interaction domain indicates \*Smad6\* MH2 domain is mainly involved in recruiting HDAC-1. Most interestingly, \*Smad6\* also binds to DNA through its MH1 domain, and the MH2 domain of \*Smad6\* masks this binding activity, indicating that \*Smad6\* MH1 and MH2 domains associate reciprocally and inhibit each other's function. \*Hoxc\*-8 induces \*Smad6\* binding to DNA as a transcriptional complex. Our findings revealed that I-Smads act as antagonists in the nucleus by recruiting HDACs.

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 DIALOG(R)File 5:Biosis Previews(R)  
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12593175 BIOSIS NO.: 200000346677

**Smad6 as a transcriptional corepressor.**

AUTHOR: Bai Shuting; Shi Xingming; Yang Xiangli; Cao Xu(a)  
 AUTHOR ADDRESS: (a)1670 University Blvd., VH G002, Birmingham, AL,  
 35294-0019\*\*USA  
 JOURNAL: Journal of Biological Chemistry 275 (12):p8267-8270 March 24,  
 2000  
 MEDIUM: print  
 ISSN: 0021-9258  
 DOCUMENT TYPE: Article  
 RECORD TYPE: Abstract  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

ABSTRACT: \*Smad6\* and Smad7, a subgroup of Smad proteins, antagonize the signals elicited by transforming growth factor-beta. These two Smads,



induced by transforming growth factor-beta...

...protein (BMP) stimulation, form stable associations with their activated type I receptors, blocking phosphorylation of receptor-regulated Smads in the cytoplasm. Here we show that \*Smad6\* interacts with homeobox (\*Hox\*) c-8 as a transcriptional corepressor, inhibiting BMP signaling in the nucleus. The interaction between \*Smad6\* and \*Hoxc\*-8 was identified by a yeast two-hybrid approach and further demonstrated by co-immunoprecipitation assays in cells. Gel shift assays show that \*Smad6\*, but not Smad7, interacts with both \*Hoxc\*-8 and \*Hoxa\*-9 as a heterodimer when binding to DNA. More importantly, the \*Smad6\*-*Hoxc\*-8* complex inhibits interaction of Smad1 with \*Hoxc\*-8- and Smad1-induced transcription activity. These data indicate that \*Smad6\* interacts with \*Hox\* transcription factors as part of the negative feedback circuit in the BMP signaling pathway.

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*Smad6\*-*Hoxc\*-8* complex

6/3,K/3 (Item 3 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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12136206 BIOSIS NO.: 199900431055

**\*Smad6\* interacts with \*Hoxc\*-8 as a transcriptional co-repressor in BMP signaling.**

AUTHOR: Bai Shuting(a); Shi Xingming(a); Yang Xiangli(a); Cao Xu(a)

AUTHOR ADDRESS: (a)Pathology, University of Alabama at Birmingham,  
Birmingham, AL\*\*USA

JOURNAL: Journal of Bone and Mineral Research 14 (SUPPL. 1):pS146 Sept., 1999

CONFERENCE/MEETING: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research St. Louis, Missouri, USA September 30-October 4, 1999

SPONSOR: American Society for Bone and Mineral Research

ISSN: 0884-0431

RECORD TYPE: Citation

LANGUAGE: English

**\*Smad6\* interacts with \*Hoxc\*-8 as a transcriptional co-repressor in BMP signaling.**

6/3,K/4 (Item 1 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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08164078 Genuine Article#: 232CA No. References: 0

**Title: \*Smad6\* interacts with \*Hoxc\*-8 as a transcriptional go-repressor in BMP signaling.**

Author(s): Bai ST; Shi XM; Yang XL; Cao X

Corporate Source: UNIV ALABAMA,/BIRMINGHAM//AL/

Journal: JOURNAL OF BONE AND MINERAL RESEARCH, 1999, V14, 1 (SEP), P 1053-1053

ISSN: 0884-0431 Publication date: 19990900

Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148

Language: English Document Type: MEETING ABSTRACT

**Title: \*Smad6\* interacts with \*Hoxc\*-8 as a transcriptional go-repressor in BMP signaling.**

6/3,K/5 (Item 1 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.

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0268006 DBA Accession No.: 2001-07760 PATENT

**Regulating bone formation, useful e.g. for treating osteoporosis, comprises**

**altering the activity of \*Smad6\* protein in forming complexes with  
\*Hoxc\*-8 - \*Smad6\* protein and \*Hoxc\*-8 protein interaction useful for  
drug screening**

AUTHOR: Cao X; Shi X; Bai S

CORPORATE SOURCE: Birmingham, AL, USA.

PATENT ASSIGNEE: Univ. Alabama 2001

PATENT NUMBER: WO 200111013 PATENT DATE: 20010215 WPI ACCESSION NO.:  
2001-191529 (2019)

PRIORITY APPLIC. NO.: US 147161 APPLIC. DATE: 19990804

NATIONAL APPLIC. NO.: WO 2000US40563 APPLIC. DATE: 20000803

LANGUAGE: English

**Regulating bone formation, useful e.g. for treating osteoporosis, comprises  
altering the activity of \*Smad6\* protein in forming complexes with  
\*Hoxc\*-8 - \*Smad6\* protein and \*Hoxc\*-8 protein interaction useful for  
drug screening**

ABSTRACT: A method for regulating bone formation is claimed. It involves a composition (A) that alters the binding activity of \*Smad6\* protein, where an increase or decrease in \*Smad6\* increases or decreases \*Smad6\*/\*Hoxc\*-8 complexes and maintains or relieves transcriptional repression of genes involved in bone formation, respectively. Also claimed are: regulating nuclear bone morphogenetic protein (BMP) signaling in an animal; screening for compounds (I) that disrupt transcriptional repression of a gene; regulating expression of gene (II) that binds \*Hoxc\*-8 by altering the level of \*Smad6\* protein where \*Smad6\* may be increased by overexpression or upregulation of its gene, and decreased by antisense hybridization of \*Smad6\* RNA; and inducing transcription of a gene (III) that encodes osteopontin, osteoprotegrin, OPGL or RANK by inhibiting \*Smad6\*. The method is used e.g. to treat osteoporosis. The interaction between \*Smad6\* and \*Hoxc\*-8 is also used as the basis for screening assays to identify compounds that disrupt transcriptional regulation of gene, to regulate expression of genes that bind \*Hoxc\*-8, and for inducing transcription of the genes for osteopontin, osteoprotegrin, OPGL or RANK. (34pp)

6/3,K/6 (Item 1 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

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134158510 CA: 134(12)158510m PATENT

**The interaction of Smad6 with Hox proteins and BMP signalling and uses thereof in regulation of bone formation**

INVENTOR(AUTHOR): Cao, Xu; Shi, Xingming; Bai, Shuting

LOCATION: USA

ASSIGNEE: Uab Research Foundation

PATENT: PCT International ; WO 0111013 A2 DATE: 20010215

APPLICATION: WO 2000US40563 (20000803) \*US PV147161 (19990804)

PAGES: 34 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-000/A

DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

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(c) 2002 Cambridge Scientific Abstracts  
File 50:CAB Abstracts 1972-2002/Apr  
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(c) 2002 BLDSC all rts. reserv.  
File 68:Env.Bib. 1974-2002/Mar  
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File 71:ELSEVIER BIOBASE 1994-2002/May W4  
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File 94:JICST-EPlus 1985-2002/Apr W1  
(c)2002 Japan Science and Tech Corp(JST)  
File 98:General Sci Abs/Full-Text 1984-2002/Apr  
(c) 2002 The HW Wilson Co.  
File 103:Energy SciTec 1974-2002/May B1  
(c) 2002 Contains copyrighted material  
File 143:Biol. & Agric. Index 1983-2002/Apr  
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File 156:ToxFile 1966-2002/Feb W4  
(c) 2002  
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File 172:EMBASE Alert 2002/May W4  
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(c) 2002 Reed Business Information Ltd.  
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(c) 1999 AAAS  
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(c) 2002 NewsRx  
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File 358:Current BioTech Abs 1983-2001/Oct  
(c) 2001 DECHEMA  
File 35:Dissertation Abs Online 1861-2002/May

(c) 2002 ProQuest Info&Learning  
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 (c) 2002 Sport Information Resource Centre  
 File 91:MANTIS(TM) 1880-2002/Jun  
 2001 (c) Action Potential  
 File 149:TGG Health&Wellness DB(SM) 1976-2002/May W3  
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 (c) 2002 BLHCIS  
 File 442:AMA Journals 1982-2002/Jun B1  
 (c)2002 Amer Med Assn -FARS/DARS apply  
 File 444:New England Journal of Med. 1985-2002/May W4  
 (c) 2002 Mass. Med. Soc.  
 File 457:The Lancet 1986-2000/Oct W1  
 (c) 2000 The Lancet, Ltd.  
 File 467:ExtraMED(tm) 2000/Dec  
 (c) 2001 Informania Ltd.

Set Items Description

S1 246 HOXC8

S2 7 S1 (S) SMAD?

S3 7 RD (unique items)

>>>KWIC option is not available in file(s): 41, 77, 399

**3/3,K/1 (Item 1 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)

(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

**135353612 CA: 135(25)353612u JOURNAL**

**Transcriptional mechanisms of bone morphogenetic protein-induced osteoprotegrin gene expression**

AUTHOR(S): Wan, Mei; Shi, Xingming; Feng, Xu; Cao, Xu

LOCATION: Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA

JOURNAL: J. Biol. Chem. DATE: 2001 VOLUME: 276 NUMBER: 13 PAGES: 10119-10125 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

**3/3,K/2 (Item 2 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)

(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

**135190556 CA: 135(14)190556n JOURNAL**

**Smad interactors in bone morphogenetic protein signaling**

AUTHOR(S): Yang, Xiangli; Cao, Xu

LOCATION: Department of Pathology, University of Alabama, Birmingham, AL, USA

JOURNAL: Methods Mol. Biol. (Totowa, NJ, U. S.) DATE: 2001 VOLUME: 177 NUMBER: Two-Hybrid Systems PAGES: 163-178 CODEN: MMBIED ISSN: 1064-3745 LANGUAGE: English PUBLISHER: Humana Press Inc.

**3/3,K/3 (Item 3 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)

(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

**134364569 CA: 134(26)364569r DISSERTATION**

**Bone morphogenetic proteins induce gene transcription and osteoblastic differentiation through the interaction between Smad1 and Hoxc-8**

AUTHOR(S): Yang, Xiangli

LOCATION: University of Alabama at Birmingham, USA

DATE: 2000 PAGES: 204 pp. CODEN: DABBBA LANGUAGE: English CITATION: Diss. Abstr. Int., B 2000, 61(3), 1234 AVAIL: UMI, Order No. DA9964660

3/3,K/4 (Item 4 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

134158510 CA: 134(12)158510m PATENT  
**The interaction of Smad6 with Hox proteins and BMP signalling and uses thereof in regulation of bone formation**  
INVENTOR(AUTHOR): Cao, Xu; Shi, Xingming; Bai, Shuting  
LOCATION: USA  
ASSIGNEE: Uab Research Foundation  
PATENT: PCT International ; WO 0111013 A2 DATE: 20010215  
APPLICATION: WO 2000US40563 (20000803) \*US PV147161 (19990804)  
PAGES: 34 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-000/A  
DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

3/3,K/5 (Item 5 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

132178572 CA: 132(14)178572v JOURNAL  
**Smad1 domains interacting with Hoxc-8 induce osteoblast differentiation**  
AUTHOR(S): Yang, Xiangli; Ji, Xiaohui; Shi, Xingming; Cao, Xu  
LOCATION: Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA  
JOURNAL: J. Biol. Chem. DATE: 2000 VOLUME: 275 NUMBER: 2 PAGES: 1065-1072 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

3/3,K/6 (Item 6 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

131098451 CA: 131(8)98451u JOURNAL  
**Smad1 interacts with homeobox DNA-binding proteins in bone morphogenetic protein signaling**  
AUTHOR(S): Shi, Xingming; Yang, Xiangli; Chen, Di; Chang, Zhijie; Cao, Xu  
LOCATION: Department of Pathology, University of Alabama School of Medicine, Birmingham, AL, 35294, USA  
JOURNAL: J. Biol. Chem. DATE: 1999 VOLUME: 274 NUMBER: 19 PAGES: 13711-13717 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

3/3,K/7 (Item 1 from file: 266)  
DIALOG(R)File 266:FEDRIP  
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00317596  
IDENTIFYING NO.: 1R01DK57501-01A1 AGENCY CODE: CRISP  
**MECHANISM OF SMAD1 MEDIATED OSTEOBLAST DIFFERENTIATION**  
PRINCIPAL INVESTIGATOR: CAO, XU  
ADDRESS: UNIV OF ALABAMA, BIRMINGHAM 1670 UNIVERSITY BLVD, VH G001 BIRMINGHAM, AL 35294-0019  
PERFORMING ORG.: UNIVERSITY OF ALABAMA AT BIRMINGHAM, BIRMINGHAM, ALABAMA  
SPONSORING ORG.: NAT INST OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES  
FY : 2001

...SUMMARY: superfamily, are potent growth factors in inducing osteoblast differentiation and stimulating bone formation. Signaling in TGF-beta

superfamily is mediated by direct phosphorylation of \*Smad\* proteins. \*Smad2\* and \*Smad3\* are phosphorylated by TGF-beta and activin receptors, whereas phosphorylation of \*Smad\* 1 is specifically induced by bone morphogenetic proteins. Upon phosphorylation these \*Smad\* proteins interact with a common partner, \*Smad4\*, and translocate into the nucleus where the complex recruits DNA binding protein(s) to activate specific gene transcription. However, the DNA binding protein(s) involved in BMP signaling has not been identified. We have demonstrated that BMPs induce the interaction of \*Smad1\* with Hoxc-8, a member of the homeodomain transcription factor family. The interaction of \*Smad\* 1 with Hoxc-8 inhibits the binding of Hoxc-8 to its DNA binding site. Hoxc-8 functions as a transcription repressor. A hox binding...

... osteopontin gene transcription is mediated through this Hox binding site. We hypothesize that BMP-2/4 induces osteoblast cell differentiation mediated by the \*Smad1\* interaction with Hoxc-8. The specific aims proposed are to: 1) characterize the specificity of the interaction between \*Smad1\* and Hox proteins in BMP2/4 signaling; 2) map domains that are responsible for the interaction between \*Smad1\* and \*Hoxc8\*. The effect of mapped \*Smad1\* interaction domains on gene transcription will also be assessed in luciferase reporter transfection studies. 3) Characterize the effects of the interaction between \*Smad1\* and Hoxc-8 on osteoblast differentiation in human primary stromal cells. Further characterization of the interaction between \*Smad1\* and Hoxc-8 will help us to understand the mechanism of BMP signaling and may yield a potential drug target to stimulate bone formation...

```

?s hoxc8
    S1      246  HOXC8
?s s1 (s) smad?
    246  S1
    10507 SMAD?
    S2      7  S1 (S) SMAD?
?rd
...completed examining records
    S3      7  RD (unique items)
?show files;ds;t/3,k/all
File  5:Biosis Previews(R) 1969-2002/May W3
    (c) 2002 BIOSIS
File  6:NTIS 1964-2002/Jun W2
    (c) 2002 NTIS, Intl Cpyrght All Rights Res
File 34:SciSearch(R) Cited Ref Sci 1990-2002/May W4
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File 103:Energy SciTec 1974-2002/May B1
    (c) 2002 Contains copyrighted material
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File 144:Pascal 1973-2002/May W4
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File 156:ToxFile 1966-2002/Feb W4
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    (c) 1999 AAAS
File 399:CA SEARCH(R) 1967-2002/UD=13622
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    (c) 2002 The HW Wilson Co.
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File 266:FEDRIP 2002/Mar
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 File 35:Dissertation Abs Online 1861-2002/May  
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 File 48:SPORTDiscus 1962-2002/Jun  
 (c) 2002 Sport Information Resource Centre  
 File 91:MANTIS(TM) 1880-2002/Jun  
 2001 (c) Action Potential  
 File 149:TGG Health&Wellness DB(SM) 1976-2002/May W3  
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 File 164:Allied & Complementary Medicine 1984-2002/May  
 (c) 2002 BLHCIS  
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 (c)2002 Amer Med Assn -FARS/DARS apply  
 File 444:New England Journal of Med. 1985-2002/May W4  
 (c) 2002 Mass. Med. Soc.  
 File 457:The Lancet 1986-2000/Oct W1  
 (c) 2000 The Lancet, Ltd.  
 File 467:ExtraMED(tm) 2000/Dec  
 (c) 2001 Informania Ltd.

Set	Items	Description
S1	246	HOXC8
S2	7	S1 (S) SMAD?
S3	7	RD (unique items)

>>>KWIC option is not available in file(s): 41, 77, 399

**3/3,K/1 (Item 1 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)

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**135353612 CA: 135(25)353612u JOURNAL**

**Transcriptional mechanisms of bone morphogenetic protein-induced osteoprotegrin gene expression**

AUTHOR(S): Wan, Mei; Shi, Xingming; Feng, Xu; Cao, Xu

LOCATION: Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA

JOURNAL: J. Biol. Chem. DATE: 2001 VOLUME: 276 NUMBER: 13 PAGES: 10119-10125 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

**3/3,K/2 (Item 2 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)

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**135190556 CA: 135(14)190556n JOURNAL**

**Smad interactors in bone morphogenetic protein signaling**

AUTHOR(S): Yang, Xiangli; Cao, Xu

LOCATION: Department of Pathology, University of Alabama, Birmingham, AL, USA

JOURNAL: Methods Mol. Biol. (Totowa, NJ, U. S.) DATE: 2001 VOLUME: 177 NUMBER: Two-Hybrid Systems PAGES: 163-178 CODEN: MMBIED ISSN: 1064-3745 LANGUAGE: English PUBLISHER: Humana Press Inc.

**3/3,K/3 (Item 3 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)

(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

**134364569 CA: 134(26)364569r DISSERTATION**

**Bone morphogenetic proteins induce gene transcription and osteoblastic**



**differentiation through the interaction between Smad1 and Hoxc-8**

AUTHOR(S): Yang, Xiangli  
LOCATION: University of Alabama at Birmingham, USA  
DATE: 2000 PAGES: 204 pp. CODEN: DABBBA LANGUAGE: English CITATION:  
Diss. Abstr. Int., B 2000, 61(3), 1234 AVAIL: UMI, Order No. DA9964660

**3/3,K/4 (Item 4 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)

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**134158510 CA: 134(12)158510m PATENT**

**The interaction of Smad6 with Hox proteins and BMP signalling and uses thereof in regulation of bone formation**

INVENTOR(AUTHOR): Cao, Xu; Shi, Xingming; Bai, Shuting  
LOCATION: USA  
ASSIGNEE: Uab Research Foundation  
PATENT: PCT International ; WO 0111013 A2 DATE: 20010215  
APPLICATION: WO 2000US40563 (20000803) \*US PV147161 (19990804)  
PAGES: 34 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-000/A  
DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN;  
CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP;  
KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO;  
NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN;  
YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM  
; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI;  
FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW;  
ML; MR; NE; SN; TD; TG

**3/3,K/5 (Item 5 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)

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**132178572 CA: 132(14)178572v JOURNAL**

**Smad1 domains interacting with Hoxc-8 induce osteoblast differentiation**

AUTHOR(S): Yang, Xiangli; Ji, Xiaohui; Shi, Xingming; Cao, Xu  
LOCATION: Department of Pathology, University of Alabama at Birmingham,  
Birmingham, AL, 35294, USA  
JOURNAL: J. Biol. Chem. DATE: 2000 VOLUME: 275 NUMBER: 2 PAGES:  
1065-1072 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER:  
American Society for Biochemistry and Molecular Biology

**3/3,K/6 (Item 6 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)

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**131098451 CA: 131(8)98451u JOURNAL**

**Smad1 interacts with homeobox DNA-binding proteins in bone morphogenetic protein signaling**

AUTHOR(S): Shi, Xingming; Yang, Xiangli; Chen, Di; Chang, Zhijie; Cao, Xu  
LOCATION: Department of Pathology, University of Alabama School of  
Medicine, Birmingham, AL, 35294, USA  
JOURNAL: J. Biol. Chem. DATE: 1999 VOLUME: 274 NUMBER: 19 PAGES:  
13711-13717 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER:  
American Society for Biochemistry and Molecular Biology

**3/3,K/7 (Item 1 from file: 266)**

DIALOG(R)File 266:FEDRIP

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00317596

IDENTIFYING NO.: 1R01DK57501-01A1 AGENCY CODE: CRISP

**MECHANISM OF SMAD1 MEDIATED OSTEOBLAST DIFFERENTIATION**

PRINCIPAL INVESTIGATOR: CAO, XU

ADDRESS: UNIV OF ALABAMA, BIRMINGHAM 1670 UNIVERSITY BLVD, VH G001

BIRMINGHAM, AL 35294-0019

PERFORMING ORG.: UNIVERSITY OF ALABAMA AT BIRMINGHAM, BIRMINGHAM, ALABAMA

SPONSORING ORG.: NAT INST OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

FY : 2001

...SUMMARY: superfamily, are potent growth factors in inducing osteoblast differentiation and stimulating bone formation. Signaling in TGF-beta superfamily is mediated by direct phosphorylation of \*Smad\* proteins. \*Smad2\* and \*Smad3\* are phosphorylated by TGF-beta and activin receptors, whereas phosphorylation of \*Smad1\* is specifically induced by bone morphogenetic proteins. Upon phosphorylation these \*Smad\* proteins interact with a common partner, \*Smad4\*, and translocate into the nucleus where the complex recruits DNA binding protein(s) to activate specific gene transcription. However, the DNA binding protein(s) involved in BMP signaling has not been identified. We have demonstrated that BMPs induce the interaction of \*Smad1\* with Hoxc-8, a member of the homeodomain transcription factor family. The interaction of \*Smad1\* with Hoxc-8 inhibits the binding of Hoxc-8 to its DNA binding site. Hoxc-8 functions as a transcription repressor. A hox binding...

... osteopontin gene transcription is mediated through this Hox binding site. We hypothesize that BMP-2/4 induces osteoblast cell differentiation mediated by the \*Smad1\* interaction with Hoxc-8. The specific aims proposed are to: 1) characterize the specificity of the interaction between \*Smad1\* and Hox proteins in BMP2/4 signaling; 2) map domains that are responsible for the interaction between \*Smad1\* and \*Hoxc8\*. The effect of mapped \*Smad1\* interaction domains on gene transcription will also be assessed in luciferase reporter transfection studies. 3) Characterize the effects of the interaction between \*Smad1\* and Hoxc-8 on osteoblast differentiation in human primary stromal cells. Further characterization of the interaction between \*Smad1\* and Hoxc-8 will help us to understand the mechanism of BMP signaling and may yield a potential drug target to stimulate bone formation...

?

=> b medline uspatfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 15:43:40 ON 01 AUG 2002

FILE 'USPATFULL' ENTERED AT 15:43:40 ON 01 AUG 2002

CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=> s hoxc()8

L1 47 HOXC(W) 8

=> dup rem l1

PROCESSING COMPLETED FOR L1

L2 47 DUP REM L1 (0 DUPLICATES REMOVED)

=> d l2 ibib abs tot

L2 ANSWER 1 OF 47 USPATFULL

ACCESSION NUMBER: 2002:157630 USPATFULL

TITLE: Inhibition of binding of hox and homeodomain-containing

proteins and uses thereof

INVENTOR(S): Cao, Xu, Birmingham, AL, UNITED STATES

Shi, Xingming, Birmingham, AL, UNITED STATES

Yang, Xiangli, Birmingham, AL, UNITED STATES

PATENT ASSIGNEE(S): UAB Research Foundation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002082235	A1	20020627
APPLICATION INFO.:	US 2001-943724	A1	20010831 (9)
RELATED APPLN. INFO.:	Division of Ser. No. US 1999-286682, filed on 5 Apr 1999, GRANTED, Pat. No. US 6284464		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-80859P	19980406 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Dr. Benjamin Adler, Adler & Associates, 8011 Candle Lane, Houston, TX, 77071	
NUMBER OF CLAIMS:	17	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	22 Drawing Page(s)	
LINE COUNT:	1328	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention demonstrates that BMP-2/4 activates osteopontin gene transcription by removing **Hoxc-8** binding through Smad1 interaction with the **Hoxc-8** DNA binding domain. Since the DNA binding domain is conserved in all Hox

and

homeodomain-containing proteins, Smad1 likely interacts with all Hox or homeodomain-containing proteins. Furthermore, the present invention reveals the Smad1-mediated transcriptional mechanism in the BMP-2/4

signaling pathway and also provides information about the transcriptional roles of the Hox genes during embryonic development.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 2 OF 47 USPATFULL

ACCESSION NUMBER: 2002:102612 USPATFULL

TITLE: Vertebrate embryonic pattern-inducing proteins

INVENTOR(S): Ingham, Philip W., Summertown, UNITED KINGDOM

McMahon, Andrew P., Lexington, MA, United States

Tabin, Clifford J., Cambridge, MA, United States

PATENT ASSIGNEE(S): President & Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)

Imperial Cancer Research Technology, Ltd., London,

UNITED KINGDOM (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6384192	B1	20020507
APPLICATION INFO.:	US 1997-957874		19971020 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1995-462386, filed on 5 Jun 1995 Continuation-in-part of Ser. No. US 1995-435093, filed on 4 May 1995, now abandoned		
Continuation-in-part	of Ser. No. US 1994-356060, filed on 14 Dec 1994, now patented, Pat. No. US 5844079 Continuation-in-part of Ser. No. US 1993-176427, filed on 30 Dec 1993, now patented, Pat. No. US 5789543		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Spector, Lorraine		
ASSISTANT EXAMINER:	Kaufman, Claire M.		
LEGAL REPRESENTATIVE:	Ropes & Gray, Vincent, Matthew P., Halstead, David P.		
NUMBER OF CLAIMS:	38		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	19 Drawing Figure(s); 19 Drawing Page(s)		
LINE COUNT:	7476		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention concerns the discovery that proteins encoded by a family of vertebrate genes, termed here hedgehog-related genes, comprise morphogenic signals produced by embryonic patterning centers, and are involved in the formation of ordered spatial arrangements of differentiated tissues in vertebrates. The present invention makes available compositions and methods that can be utilized, for example to generate and/or maintain an array of different vertebrate tissue both in vitro and in vivo.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 3 OF 47 MEDLINE

ACCESSION NUMBER: 2002113327 MEDLINE

DOCUMENT NUMBER: 21683518 PubMed ID: 11711531

TITLE: A nuclear antagonistic mechanism of inhibitory Smads in transforming growth factor-beta signaling.

AUTHOR: Bai Shuting; Cao Xu

CORPORATE SOURCE: Department of Pathology, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama 35294, USA.

CONTRACT NUMBER: DK 53757 (NIDDK)

DK 57501 (NIDDK)

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Feb 8) 277 (6) 4176-82.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200203  
ENTRY DATE: Entered STN: 20020216  
Last Updated on STN: 20020307  
Entered Medline: 20020305

AB Inhibitory Smads (I-Smads), including Smad6 and Smad7, were initially characterized as cytoplasmic antagonists in the transforming growth factor-beta signaling pathway. However, I-Smads are also localized in the nucleus. Previously, we have shown that Smad6 can function as a transcriptional co-repressor. In this study, we found both Smad6 and

Smad7

interact with histone deacetylases (HDACs). Acetylation state of core histones plays a critical role in gene transcription regulation. An HDAC inhibitor, trichostatin A, released Smad6-mediated transcription repression. Moreover, class I HDACs (HDAC-1 and -3), not class II HDACs (HDAC-4, -5, and -6), were co-immunoprecipitated with Smad6. Endogenous HDAC-1 was also shown to interact with both Smad6 and **Hoxc-**

**8**. Mapping of the interaction domain indicates Smad6 MH2 domain is mainly involved in recruiting HDAC-1. Most interestingly, Smad6 also

binds

to DNA through its MH1 domain, and the MH2 domain of Smad6 masks this binding activity, indicating that Smad6 MH1 and MH2 domains associate reciprocally and inhibit each other's function. **Hoxc-8** induces Smad6 binding to DNA as a transcriptional complex. Our findings revealed that I-Smads act as antagonists in the nucleus by recruiting HDACs.

L2 ANSWER 4 OF 47 MEDLINE  
ACCESSION NUMBER: 2002201380 IN-PROCESS  
DOCUMENT NUMBER: 21931096 PubMed ID: 11934149  
TITLE: Colinearity and non-colinearity in the expression of Hox genes in developing chick skin.  
AUTHOR: Reid Alasdair I; Gaunt Stephen J  
CORPORATE SOURCE: Department of Developmental Genetics and Imprinting, The Babraham Institute, Cambridge, UK.  
SOURCE: INTERNATIONAL JOURNAL OF DEVELOPMENTAL BIOLOGY, (2002 Mar) 46 (2) 209-15.  
Journal code: 8917470. ISSN: 0214-6282.

PUB. COUNTRY: Spain  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals  
ENTRY DATE: Entered STN: 20020406  
Last Updated on STN: 20020406

AB Hox genes are usually expressed temporally and spatially in a colinear manner with respect to their positions in the Hox complex. We found that these characteristics apply to several Hox genes expressed in developing chick skin (**Hoxb-4**, **Hoxa-7** and **Hoxc-8**), and we classed this group of genes as regionally restricted. To our surprise, we found that most of the Hox genes we examined are regionally unrestricted in their expression in the embryonic chick skin. This second group includes the **Hoxd** genes, **Hoxd-4** to **Hoxd-13**, **Hoxa-11** and **Hoxc-6**. Temporally, the expression of the regionally restricted genes can be observed by E5

within

the epidermis, whereas the spatially unrestricted genes are not expressed in the epidermis until E6.25. Unexpectedly, we found that all the unrestricted genes are expressed concomitantly and therefore do not conform to temporal colinearity. Moreover, the dermal expression for both groups occurs later, but maintains the same anteroposterior patterning to that seen previously in the epidermis. During embryonic day 7-8, expression for all genes is up-regulated within the dense dermis whilst being reduced within the inter-bud regions. Later expression within the bud mesenchyme is down-regulated whilst high levels of transcriptional

activity are detectable within the epidermal sheath of each feather bud. These results indicate that the transcriptional activity of Hox genes in the developing chick skin could be important during embryonic skin patterning both by providing regionally restricted positional cues, and also by imparting generic signals necessary for feather morphology.

L2 ANSWER 5 OF 47 USPATFULL

ACCESSION NUMBER: 2001:147676 USPATFULL  
TITLE: Inhibition of binding of Hox and  
homeodomain-containing  
proteins and uses thereof  
INVENTOR(S): Cao, Xu, Birmingham, AL, United States  
Shi, Xingming, Birmingham, AL, United States  
Yang, Xiangli, Birmingham, AL, United States  
PATENT ASSIGNEE(S): UAB Research Foundation, Birmingham, AL, United States  
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6284464	B1	20010904
APPLICATION INFO.:	US 1999-286682		19990405 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-80859P	19980406 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Schwartzman, Robert A.	
LEGAL REPRESENTATIVE:	Adler, Benjamin Aaron	
NUMBER OF CLAIMS:	6	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	28 Drawing Figure(s); 22 Drawing Page(s)	
LINE COUNT:	1183	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention demonstrates that BMP-2/4 activates osteopontin gene transcription by removing **Hoxc-8** binding through Smad1 interaction with the **Hoxc-8** DNA binding domain. Since the DNA binding domain is conserved in all Hox and homeodomain-containing proteins, Smad1 likely interacts with all Hox or homeodomain-containing proteins. Furthermore, the present invention reveals the Smad1-mediated transcriptional mechanism in the BMP-2/4 signaling pathway and also provides information about the transcriptional roles of the Hox genes during embryonic development.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 6 OF 47 USPATFULL

ACCESSION NUMBER: 2001:126124 USPATFULL  
TITLE: Nucleic acids encoding hedgehog proteins  
INVENTOR(S): Ingham, Philip W., Summertown, United Kingdom  
McMahon, Andrew P., Lexington, MA, United States  
Tabin, Clifford J., Cambridge, MA, United States  
PATENT ASSIGNEE(S): President & Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)  
Imperial Cancer Research Technology, Ltd., United Kingdom (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6271363	B1	20010807
APPLICATION INFO.:	US 1997-954698		19971020 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1995-462386, filed on 5 Jun 1995 Continuation-in-part of Ser. No. US 1995-435093, filed on 4 May 1995 Continuation-in-part of Ser. No.		

US

1994-356060, filed on 14 Dec 1994, now patented, Pat.  
No. US 5844079 Continuation-in-part of Ser. No. US  
1993-176427, filed on 30 Dec 1993, now patented, Pat.  
No. US 5789543

DOCUMENT TYPE: Utility  
FILE SEGMENT: GRANTED  
PRIMARY EXAMINER: Spector, Lorraine  
ASSISTANT EXAMINER: Kaufman, Claire M.  
LEGAL REPRESENTATIVE: Foley, Hoag & Eliot, LLP, Vincent, Matthew P., Varma,  
Anita  
NUMBER OF CLAIMS: 38  
EXEMPLARY CLAIM: 2  
NUMBER OF DRAWINGS: 19 Drawing Figure(s); 19 Drawing Page(s)  
LINE COUNT: 7491

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention concerns the discovery that proteins encoded by a  
family of vertebrate genes, termed here hedgehog-related genes,  
comprise

morphogenic signals produced by embryonic patterning centers, and are  
involved in the formation of ordered spatial arrangements of  
differentiated tissues in vertebrates. The present invention makes  
available compositions and methods that can be utilized, for example to  
generate and/or maintain an array of different vertebrate tissue both  
in  
vitro and in vivo.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 7 OF 47 USPATFULL

ACCESSION NUMBER: 2001:112054 USPATFULL  
TITLE: Screening assays for hedgehog agonists and antagonists  
INVENTOR(S): Marigo, Valeria, Brookline, MA, United States  
Tabin, Clifford J., Cambridge, MA, United States  
Ingham, Philip W., Summertown, United Kingdom  
McMahon, Andrew P., Lexington, MA, United States  
PATENT ASSIGNEE(S): Imperial Cancer Res. Technology, United Kingdom  
(non-U.S. corporation)  
President & Fellows of Harvard College, Cambridge, MA,  
United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6261786	B1	20010717
APPLICATION INFO.:	US 1996-674509		19960702 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1995-460900, filed on 5 Jun 1995, now patented, Pat. No. US 6156747 Continuation-in-part of Ser. No. US 1995-462386, filed on 5 Jun 1995 Continuation-in-part of Ser. No. US 1995-435093, filed on 4 May 1995, now abandoned Continuation-in-part of Ser. No. US 1994-356060, filed on 14 Dec 1994, now patented, Pat. No. US 5844079 Continuation-in-part of Ser. No. US 1993-176427, filed on 30 Dec 1993, now patented, Pat. No. US 5789543		

DOCUMENT TYPE: Utility  
FILE SEGMENT: GRANTED  
PRIMARY EXAMINER: Kunz, Gary L.  
ASSISTANT EXAMINER: Kaufman, Claire M.  
LEGAL REPRESENTATIVE: Ropes & Gray  
NUMBER OF CLAIMS: 27  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 25 Drawing Figure(s); 21 Drawing Page(s)  
LINE COUNT: 8121

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention concerns the discovery that proteins encoded by a  
family of vertebrate genes, termed here hedgehog-related genes,  
comprise

morphogenic signals produced by embryonic patterning centers, and are involved in the formation of ordered spatial arrangements of differentiated tissues in vertebrates. The present invention makes available compositions and methods that can be utilized, for example to generate and/or maintain an array of different vertebrate tissue both in vitro and in vivo.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 8 OF 47 USPATFULL

ACCESSION NUMBER: 2001:59611 USPATFULL  
TITLE: Yeast-bacteria shuttle vector  
INVENTOR(S): Bradshaw, M. Suzanne, Cincinnati, OH, United States  
Bollekens, Jacques A., Brussels, Belgium  
Ruddle, Frank H., New Haven, CT, United States  
PATENT ASSIGNEE(S): Yale University, New Haven, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6221588	B1	20010424
APPLICATION INFO.:	US 1998-95372		19980610 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1996-761704, filed on 6 Dec 1996, now patented, Pat. No. US 5866404		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-8250P	19951206 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Yucel, Remy	
LEGAL REPRESENTATIVE:	Morgan & Finnegan, L.L.P.	
NUMBER OF CLAIMS:	6	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	8 Drawing Figure(s); 5 Drawing Page(s)	
LINE COUNT:	850	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The functional analysis of genes frequently requires the manipulation of large genomic regions. A yeast-bacteria shuttle vector is described, that can be used to clone large regions of DNA by homologous recombination. The important feature of present invention is the presence of the a bacterial replication origin, which allows large DNA insert capacity. The utility of this vector lies in its ability to isolate, manipulate and maintain large fragments in bacteria and yeast, allowing for mutagenesis by yeast genetics and simplified preparation of plasmid DNA in bacteria.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 9 OF 47 MEDLINE

ACCESSION NUMBER: 2001495060 MEDLINE  
DOCUMENT NUMBER: 21413903 PubMed ID: 11432851  
TITLE: An Abd-B class HOX.PBX recognition sequence is required for expression from the mouse Ren-1c gene.  
AUTHOR: Pan L; Xie Y; Black T A; Jones C A; Pruitt S C; Gross K W  
CORPORATE SOURCE: Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Buffalo, New York 14263, USA.  
CONTRACT NUMBER: CA16056 (NCI)  
HD36416 (NICHD)  
HL48459 (NHLBI)  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Aug 31) 276 (35)



32489-94.  
Journal code: 2985121R. ISSN: 0021-9258.

• PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200110  
ENTRY DATE: Entered STN: 20010910  
Last Updated on STN: 20011022  
Entered Medline: 20011018

AB Expression from the mouse Ren-1(c) gene in As4.1 cells is dependent on a proximal promoter element (PPE) located at approximately -60 and a 241-base pair enhancer region located at -2625 relative to the transcription start site. The PPE (TAATAAATCAA) is identical to a consensus HOX.PBX binding sequence. Further, PBX1b has been shown to be a component of a PPE-specific binding complex present in nuclear extracts from As4.1 cells. The binding affinities of different paralog HOX members to the PPE were examined in the absence or presence of PBX1b. HOXB6, -B7, and -C8 failed to bind the PPE alone but showed weak affinity in the presence of PBX1b. In contrast, HOXD10 and to a lesser degree HOXB9 bound the PPE with high affinities regardless of whether PBX1b was present. Abd-B HOX members, including HOXD10, -A10, -A9, -B9, and -C9, are expressed in As4.1 cells. The ability of HOX and PBX1b to form a ternary complex with PREP1 on the PPE is also demonstrated both in vivo and in vitro. Point mutations in either the HOX or PBX half-site of the PPE disrupted the formation of the HOX.PBX complex and dramatically decreased transcriptional activity of the Ren-1(c) gene demonstrating that both the HOX and PBX half-sites are critical for mouse renin gene expression.

These results strongly implicate Abd-B class Hox genes and their cofactors as major determinants of the sites of renin expression.

L2 ANSWER 10 OF 47 MEDLINE  
ACCESSION NUMBER: 2001169891 MEDLINE  
DOCUMENT NUMBER: 21167819 PubMed ID: 11139569  
TITLE: Transcriptional mechanisms of bone morphogenetic protein-induced osteoprotegerin gene expression.  
AUTHOR: Wan M; Shi X; Feng X; Cao X  
CORPORATE SOURCE: Department of Pathology, University of Alabama at Birmingham, 35294, USA.  
CONTRACT NUMBER: DK 53757 (NIDDK)  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Mar 30) 276 (13) 10119-25.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200105  
ENTRY DATE: Entered STN: 20010517  
Last Updated on STN: 20010517  
Entered Medline: 20010510

AB Osteoprotegerin (OPG), an osteoblast-secreted decoy receptor, specifically binds to osteoclast differentiation factor and inhibits osteoclast maturation. Members of the transforming growth factor-beta superfamily including bone morphogenetic proteins (BMPs) stimulate OPG mRNA expression. In this study, we have characterized the transcription mechanism of BMP-induced OPG gene expression. Transfection of Smad1 and a constitutively active BMP type IA receptor ALK3 (Q233) stimulated the OPG promoter. Deletion analysis of the OPG promoter identified two **Hoxc-8** binding sites that respond to BMP stimulation. Glutathione S-transferase-**Hoxc-8** protein binds to these two Hox sites specifically. Consistent with the transfection results of the native promoter, ALK3 or Smad1 linker region, which interacts with

**Hoxc-8**, stimulated the activation of the reporter construct with the two Hox sites. Overexpression of **Hoxc-8** inhibited the induced promoter activity. When the two Hox binding sites were mutated, ALK3 or Smad1 linker region no longer activated the transcription. Importantly, Smad1 linker region induced both OPG promoter activity and endogenous OPG protein expression in 2T3 osteoblastic cells. The medium from cells transfected with Smad1 linker region expression plasmid effectively inhibited osteoclastogenesis. Collectively, our data indicate that Hox sites mediate both OPG promoter construct activity and endogenous OPG gene expression in response to BMP stimulation.

L2 ANSWER 11 OF 47 MEDLINE  
 ACCESSION NUMBER: 2001222113 MEDLINE  
 DOCUMENT NUMBER: 21211305 PubMed ID: 11311170  
 TITLE: Axial skeletal patterning in mice lacking all paralogous group 8 Hox genes.  
 AUTHOR: van den Akker E; Fromental-Ramain C; de Graaff W; Le Mouellic H; Brulet P; Chambon P; Deschamps J  
 CORPORATE SOURCE: Hubrecht Laboratory, The Netherlands Institute for Developmental Biology, Uppsalalaan 8, Utrecht, The Netherlands.. jacqueli@niob.knaw.nl  
 SOURCE: DEVELOPMENT, (2001 May) 128 (10) 1911-21.  
 Journal code: 8701744. ISSN: 0950-1991.  
 PUB. COUNTRY: England: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200106  
 ENTRY DATE: Entered STN: 20010625  
 Last Updated on STN: 20010625  
 Entered Medline: 20010621

AB We present a detailed study of the genetic basis of mesodermal axial patterning by paralogous group 8 Hox genes in the mouse. The phenotype of Hoxd8 loss-of-function mutants is presented, and compared with that of Hoxb8- and Hoxc8-null mice. Our analysis of single mutants reveals common features for the Hoxc8 and Hoxd8 genes in patterning lower thoracic and lumbar vertebrae. In the Hoxb8 mutant, more anterior axial regions are affected. The three paralogous Hox genes are expressed up to similar rostral boundaries in the mesoderm, but at levels that strongly vary with the axial position. We find that the axial region affected in each of the single mutants mostly corresponds to the area with the highest level of gene expression. However, analysis of double and triple mutants reveals that lower expression of the other two paralogous genes also plays a patterning role when the mainly expressed gene is defective. We therefore conclude that paralogous group 8 Hox genes are involved in patterning quite an extensive anteroposterior (AP) axial region. Phenotypes of double and triple mutants reveal that Hoxb8, Hoxc8 and Hoxd8 have redundant functions at upper thoracic and sacral levels, including positioning of the hindlimbs. Interestingly, loss of functional Hoxb8 alleles partially rescues the phenotype of Hoxc8- and Hoxc8/Hoxd8-null mutants at lower thoracic and lumbar levels. This suggests that Hoxb8 affects patterning at these axial positions differently from the other paralogous gene products. We conclude that paralogous Hox genes can have a unique role in patterning specific axial regions in addition to their redundant function at other AP levels.

L2 ANSWER 12 OF 47 MEDLINE  
 ACCESSION NUMBER: 2001112735 MEDLINE  
 DOCUMENT NUMBER: 20576440 PubMed ID: 11042172

TITLE: Hoxa-9 represses transforming growth factor-beta-induced osteopontin gene transcription.  
AUTHOR: Shi X; Bai S; Li L; Cao X  
CORPORATE SOURCE: Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA.  
CONTRACT NUMBER: DK53757 (NIDDK)  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jan 5) 276 (1) 850-5.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200102  
ENTRY DATE: Entered STN: 20010322  
Last Updated on STN: 20010322  
Entered Medline: 20010208

AB Smad2 and Smad3 are downstream transforming growth factor-beta (TGF-beta) signaling molecules. Upon phosphorylation by its type I receptor, Smad2 or Smad3 forms a complex with Smad4 and translocates to the nucleus where the complex activates target gene transcription. In the present study, we report that Smad3 binds directly to the osteopontin (OPN) promoter and that Smad4 interacts with the Hox protein and displaces it from its cognate DNA binding site in response to TGF-beta stimulation. In gel shift assays, the glutathione S-transferase-Smad3 fusion protein was found to bind to a 50-base pair DNA element (-179 to -229) from the OPN promoter. Also, we found that both **Hoxc-8** and Hoxa-9 bound to a Hox binding site adjacent to Smad3 binding sequence. Interestingly, Smad4, the common partner for both bone morphogenic protein and TGF-beta signaling pathways, inhibited the binding of Hox protein to DNA. FLAG-tagged Smad4 coimmunoprecipitated with HA-tagged Hoxa-9 from cotransfected COS-1 cells, demonstrating an interaction between Smad4 and Hoxa-9. Transfection studies showed that Hoxa-9 is a strong transcriptional repressor; it suppresses the transcription of the luciferase reporter gene driven by a 124-base pair OPN promoter fragment containing both Smad3 and Hox binding sites. Taken together, these data demonstrate a unique TGF-beta-induced transcription mechanism. Smad3 and Smad4 exhibit different functions in activation of OPN transcription. Smad3 binds directly to the OPN promoter as a sequence-specific activator, and Smad4 displaces the transcription repressor, Hoxa-9, by formation of Smad4/Hox complex as part of the transcription mechanism in response to TGF-beta stimulation.

L2 ANSWER 13 OF 47 MEDLINE  
ACCESSION NUMBER: 2001444268 MEDLINE  
DOCUMENT NUMBER: 21382937 PubMed ID: 11489599  
TITLE: (14)C methanol incorporation into DNA and proteins of organogenesis stage mouse embryos in vitro.  
AUTHOR: Huang Y S; Held G A; Andrews J E; Rogers J M  
CORPORATE SOURCE: Experimental Toxicology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, NC 27711, USA.  
SOURCE: REPRODUCTIVE TOXICOLOGY, (2001 Jul-Aug) 15 (4) 429-35.  
Journal code: 8803591. ISSN: 0890-6238.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200110  
ENTRY DATE: Entered STN: 20010813

- AB Methanol (MeOH), a widely used industrial solvent and alternative motor fuel, has been shown to be mutagenic and teratogenic. We have demonstrated that methanol is teratogenic in mice in vivo and causes dysmorphogenesis in cultured organogenesis stage mouse embryos. Although MeOH is a product of endogenous metabolism in the gut and can be found in humans following consumption of various foods, elevated levels of methanol could lead to methylation of cellular macromolecules. DNA methylation has been demonstrated to suppress transcription of fetal genes and may also play an important role in genetic imprinting. Embryonal proteins are also potential targets for methanol-induced methylation. We investigated the potential of administered methanol to incorporate into and/or alter the methylation of embryonal DNA or to affect specific protein methylation. Gestational day 8 CD-1 mouse embryos were grown for 24 h in culture medium (CM) with 0, 4, or 8 mg MeOH + 20 microCi (14)C-MeOH/mL. At the end of the culture period, yolk sacs and embryos were separated for each treatment group. The DNA was purified by cesium chloride gradient centrifugation in the presence of ethidium bromide and (14)C incorporation was determined. Methylation of a selected gene, **Hoxc-8**, was assessed by using methylation-specific restriction enzymes. The (14)C activity was found superimposed over the DNA-containing fraction, indicating incorporation. DNA from embryos treated with 4 mg MeOH/mL CM gave the highest incorporation of (14)C-MeOH (8 mg/mL was growth inhibiting). Methylation of **Hoxc-8** appeared to be increased in embryos treated with 4 mg MeOH/mL CM, but not in embryos treated with 8 mg MeOH/mL. Lack of incorporation of methylation at the higher concentration may be due to the failure of embryos to grow at this concentration of MeOH. The incorporation of (14)C-MeOH into embryo proteins was investigated by polyacrylamide gel electrophoresis (PAGE) and autoradiography. Incorporation of (14)C-MeOH into specific proteins was observed but the labeling specificity was not methanol dose-related. These results indicate that methyl groups from (14)C-MeOH are incorporated into mouse embryo DNA and protein. Our results further suggest that methanol exposure may increase genomic methylation under certain conditions which could lead to altered gene expression.

L2 ANSWER 14 OF 47 MEDLINE

ACCESSION NUMBER: 2001454418 MEDLINE

DOCUMENT NUMBER: 21391686 PubMed ID: 11500978

TITLE: Anterior expression of the caudal homologue cCdx-B activates a posterior genetic program in avian embryos.

AUTHOR: Ehrman L A; Yutzey K E

CORPORATE SOURCE: Division of Molecular Cardiovascular Biology, The Children's Hospital Research Foundation, Cincinnati, Ohio 45229, USA.

CONTRACT NUMBER: HL57219 (NHLBI)  
T32 HL07752 (NHLBI)SOURCE: DEVELOPMENTAL DYNAMICS, (2001 Aug) 221 (4) 412-21.  
Journal code: 9201927. ISSN: 1058-8388.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200111

ENTRY DATE: Entered STN: 20010814

Last Updated on STN: 20011105

Entered Medline: 20011101

- AB Several families of regulatory genes have been implicated in anteroposterior patterning of gastrulation-stage vertebrate embryos.

Members of the *Drosophila* caudal family of homeobox genes (Cdx) are among the earliest regulators of posterior cell fates. The regulatory cascade initiated by the caudal homologue, cCdx-B, was examined in avian embryos. During gastrulation, cCdx-B is expressed with other posterior patterning genes. In the posterior primitive streak, cCdx-B expression coincides with posteriorly expressed Hox cluster genes and Wnt family members such as Wnt-8c. The hierarchical relationship between these patterning genes was examined after anterior ectopic expression of cCdx-B. cCdx-B expression in anterior cardiogenic cells by means of adenoviral infection leads to the induction of Wnt-8c and the posterior Hox genes, *Hoxa-7*, *Hoxc-6*, and **Hoxc-8**. Cardiogenesis is not inhibited in cCdx-B expressing anterior lateral mesoderm, indicating that anterior cell fates are not respecified with the activation of posterior patterning genes after gastrulation. These results support an important role for cCdx-B in initiating a posterior program of gene expression that includes Wnt signaling molecules and the Hox cluster genes.

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L2 ANSWER 15 OF 47 MEDLINE  
 ACCESSION NUMBER: 2001118875 MEDLINE  
 DOCUMENT NUMBER: 20570143 PubMed ID: 11120606  
 TITLE: TGFbeta and BMP-2 activation of the OPN promoter: roles of smad- and hox-binding elements.  
 AUTHOR: Hullinger T G; Pan Q; Viswanathan H L; Somerman M J  
 CORPORATE SOURCE: Cardiovascular Therapeutics, Pfizer Inc., Ann Arbor, Michigan, 48105, USA.  
 SOURCE: EXPERIMENTAL CELL RESEARCH, (2001 Jan 1) 262 (1) 69-74.  
 Journal code: 0373226. ISSN: 0014-4827.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200102  
 ENTRY DATE: Entered STN: 20010322  
 Last Updated on STN: 20010322  
 Entered Medline: 20010215

AB Members of the transforming growth factor superfamily are known to transduce signals via the activation of Smad proteins. Ligand binding to transmembrane cell surface receptors triggers the phosphorylation of pathway-specific Smads. These Smads then complex with Smad 4 and are translocated to the nucleus where they effect gene transcription. Smads 1 and 4 were recently demonstrated to mediate BMP activation of the OPN promoter by inhibiting the interaction of **Hoxc-8** protein with a Hox-binding element. While previous studies have indicated that specific DNA sequences are recognized by Smad complexes in several promoters, the role of Smad-binding elements (SBEs) in activation of the OPN promoter by members of the TGFbeta superfamily has not been

previously evaluated. In this study we tested the hypothesis that a putative Smad-binding region containing the sequence AGACTGTCTGGAC is involved in the activation of the OPN promoter by members of the TGFbeta superfamily. Functional analyses demonstrated that the both the HBE- and Smad-binding region were involved in BMP-2-induced activation of the promoter, whereas, the HBE appeared to be the primary region involved in activation by TGFbeta. Deletion of the first 9 bases in the Smad-binding region substantially reduced BMP-2-mediated activation of the promoter. These results strongly suggest that both the Hox- and the Smad-binding regions play a role in BMP-2-induced activation of the OPN promoter.

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L2 ANSWER 16 OF 47 USPATFULL  
 ACCESSION NUMBER: 2000:174376 USPATFULL  
 TITLE: Nucleic acids encoding hedgehog proteins

INVENTOR(S): Ingham, Philip W., Summertown, United Kingdom  
McMahon, Andrew P., Lexington, MA, United States  
Tabin, Clifford J., Cambridge, MA, United States  
Bumcrot, David A., Belmont, MA, United States  
PATENT ASSIGNEE(S): Marti-Gorostiza, Elisa, Brookline, MA, United States  
President & Fellows of Harvard College, Cambridge, MA,  
United States (U.S. corporation)  
Imperial Cancer Research Technology, Ltd., United  
Kingdom (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6165747		20001226
APPLICATION INFO.:	US 1995-460900		19950605 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1995-435093, filed on 4 May 1995 which is a continuation-in-part of Ser. No. US 1994-356060, filed on 14 Dec 1994, now		

patented,

Pat. No. US 5844079 which is a continuation-in-part of  
Ser. No. US 1993-176427, filed on 30 Dec 1993, now  
patented, Pat. No. US 5789543

DOCUMENT TYPE: Utility  
FILE SEGMENT: Granted  
PRIMARY EXAMINER: Kunz, Gary L.  
ASSISTANT EXAMINER: Kaufman, Claire M.  
LEGAL REPRESENTATIVE: Foley, Hoag & Eliot, LLP, Vincent, Matthew P., Varma,  
Anita  
NUMBER OF CLAIMS: 50  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 19 Drawing Page(s)  
LINE COUNT: 9236

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention concerns the discovery that proteins encoded by a  
family of vertebrate genes, termed here hedgehog-related genes,  
comprise

morphogenic signals produced by tissue patterning centers, and are  
involved in the formation of ordered spatial arrangements of  
differentiated tissues in vertebrates. The present invention makes  
available compositions and methods that can be utilized, for example to  
generate and/or maintain an array of different vertebrate tissue both  
in  
vitro and in vivo.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 17 OF 47 MEDLINE  
ACCESSION NUMBER: 2000187528 MEDLINE  
DOCUMENT NUMBER: 20187528 PubMed ID: 10722652  
TITLE: Smad6 as a transcriptional corepressor.  
AUTHOR: Bai S; Shi X; Yang X; Cao X  
CORPORATE SOURCE: Department of Pathology, University of Alabama School of  
Medicine, Birmingham, Alabama 35294, USA.  
CONTRACT NUMBER: DK53757 (NIDDK)  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12)  
8267-70.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200004  
ENTRY DATE: Entered STN: 20000505  
Last Updated on STN: 20000505  
Entered Medline: 20000427

AB Smad6 and Smad7, a subgroup of Smad proteins, antagonize the signals  
elicited by transforming growth factor-beta. These two Smads, induced by

transforming growth factor-beta or bone morphogenetic protein (BMP) stimulation, form stable associations with their activated type I receptors, blocking phosphorylation of receptor-regulated Smads in the cytoplasm. Here we show that Smad6 interacts with homeobox (Hox) c-8 as a transcriptional corepressor, inhibiting BMP signaling in the nucleus. The interaction between Smad6 and **Hoxc-8** was identified by a yeast two-hybrid approach and further demonstrated by co-immunoprecipitation assays in cells. Gel shift assays show that Smad6, but not Smad7, interacts with both **Hoxc-8** and Hoxa-9 as a heterodimer when binding to DNA. More importantly, the Smad6-**Hoxc-8** complex inhibits interaction of Smad1 with **Hoxc-8**- and Smad1-induced transcription activity. These data indicate that Smad6 interacts with Hox transcription factors as part of the negative feedback circuit in the BMP signaling pathway.

L2 ANSWER 18 OF 47 MEDLINE  
 ACCESSION NUMBER: 2001091548 MEDLINE  
 DOCUMENT NUMBER: 20515610 PubMed ID: 11060235  
 TITLE: Loss- and gain-of-function mutations show a polycomb group function for Ring1A in mice.  
 AUTHOR: del Mar Lorente M; Marcos-Gutierrez C; Perez C; Schoorlemmer J; Ramirez A; Magin T; Vidal M  
 CORPORATE SOURCE: Developmental and Cell Biology, Centro de Investigaciones Biologicas, Velazquez 144, Spain.  
 SOURCE: DEVELOPMENT, (2000 Dec) 127 (23) 5093-100.  
 Journal code: 8701744. ISSN: 0950-1991.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200101  
 ENTRY DATE: Entered STN: 20010322  
 Last Updated on STN: 20010322  
 Entered Medline: 20010125

AB The products of the Polycomb group (PcG) of genes act as transcriptional repressors involved in the maintenance of homeotic gene expression patterns throughout development, from flies to mice. Biochemical and molecular evidence suggests that the mouse Ring1A gene is a member of the PcG of genes. However, genetic evidence is needed to establish PcG function for Ring1A, since contrary to all other murine PcG genes, there is no known Drosophila PcG gene encoding a homolog of the Ring1A protein. To study Ring1A function we have generated a mouse line lacking Ring1A

and

mouse lines overexpressing Ring1A. Both Ring1A(-/-) and Ring1A(+/-) mice show anterior transformations and other abnormalities of the axial skeleton, which indicates an unusual sensitivity of axial skeleton patterning to Ring1A gene dosage. Ectopic expression of Ring1A also results in dose-dependent anterior transformations of vertebral identity, many of which, interestingly, are shared by Ring1A(-/-) mice. In

contrast,

the alterations of Hox gene expression observed in both type of mutant mice are subtle and involve a reduced number of Hox genes. Taken

together,

these results provide genetic evidence for a PcG function of the mouse Ring1A gene.

L2 ANSWER 19 OF 47 MEDLINE  
 ACCESSION NUMBER: 2000092875 MEDLINE  
 DOCUMENT NUMBER: 20092875 PubMed ID: 10625647  
 TITLE: Smad1 domains interacting with **Hoxc-8** induce osteoblast differentiation.  
 AUTHOR: Yang X; Ji X; Shi X; Cao X  
 CORPORATE SOURCE: Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA.  
 CONTRACT NUMBER: DK53757 (NIDDK)  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Jan 14) 275 (2)

1065-72.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; Space Life Sciences  
ENTRY MONTH: 200002  
ENTRY DATE: Entered STN: 20000309  
Last Updated on STN: 20000309  
Entered Medline: 20000218

AB Bone morphogenetic proteins are potent osteotropic agents that induce osteoblast differentiation and bone formation. The signal transduction of bone morphogenetic proteins has recently been discovered to involve Smad proteins. Smad1 is an essential intracellular component that is specifically phosphorylated by bone morphogenetic protein receptors and translocated into the nucleus upon ligand stimulation. Previously, we have

reported that Smad1 activates osteopontin gene expression in response to bone morphogenetic protein stimulation through an interaction with a homeodomain transcription factor, **Hoxc-8**. In the present study, the interaction domains between the two proteins were characterized by deletional analysis in both yeast two-hybrid and gel shift assays. Two regions within the amino-terminal 87 amino acid residues

of Smad1 were mapped to interact with **Hoxc-8**, one of which binds to the homeodomain. Overexpression of recombinant cDNAs encoding the **Hoxc-8** interaction domains of Smad1 effectively activated osteopontin gene transcription in transient transfection assays. Furthermore, stable expression of these Smad1 fragments in 2T3 osteoblast precursor cells stimulated osteoblast differentiation-related gene expression and led to mineralized bone matrix

formation. Our data suggest that the interaction of amino-terminal Smad1 with **Hoxc-8** mimics bone morphogenetic protein signaling and is sufficient to induce osteoblast differentiation and bone cell formation.

L2 ANSWER 20 OF 47 MEDLINE

ACCESSION NUMBER: 2000470713 MEDLINE

DOCUMENT NUMBER: 20347555 PubMed ID: 10888842

TITLE: An induction gene trap for identifying a homeoprotein-regulated locus.

AUTHOR: Mainguy G; Montesinos M L; Lesaffre B; Zevnik B; Karasawa M; Kothary R; Wurst W; Prochiantz A; Volovitch M

CORPORATE SOURCE: CNRS, UMR 8542, Ecole Normale Supérieure, 46 rue d'Ulm, 75230 Paris Cedex 05 France.

SOURCE: NATURE BIOTECHNOLOGY, (2000 Jul) 18 (7) 746-9.  
Journal code: 9604648. ISSN: 1087-0156.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200010  
ENTRY DATE: Entered STN: 20001012  
Last Updated on STN: 20010517  
Entered Medline: 20001005

AB An important issue in developmental biology is the identification of homeoprotein target genes. We have developed a strategy based on the internalization and nuclear addressing of exogenous homeodomains, using an

engrailed homeodomain (EnHD) to screen an embryonic stem (ES) cell gene trap library. Eight integrated gene trap loci responded to EnHD. One is within the bullous pemphigoid antigen 1 (BPAG1) locus, in a region that interrupts two neural isoforms. By combining in vivo electroporation with organotypic cultures, we show that an already identified BPAG1 enhancer/promoter is differentially regulated by homeoproteins



**Hoxc-8** and Engrailed in the embryonic spinal cord and mesencephalon. This strategy can therefore be used for identifying and mutating homeoprotein targets. Because homeodomain third helices can internalize proteins, peptides, phosphopeptides, and antisense oligonucleotides, this strategy should be applicable to other intracellular targets for characterizing genetic networks involved in a large number of physiopathological states.

L2 ANSWER 21 OF 47 USPATFULL

ACCESSION NUMBER: 1999:132504 USPATFULL  
 TITLE: Genome anthologies for harvesting gene variants  
 INVENTOR(S): Ruano, Gualberto, New Haven, CT, United States  
 Bentley, Kevin L., Madison, CT, United States  
 Ruddie, Frank H., New Haven, CT, United States  
 PATENT ASSIGNEE(S): Genaissance Pharmaceuticals, New Haven, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5972614		19991026
APPLICATION INFO.:	US 1997-987966		19971210 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1996-761704, filed on 6 Dec 1996, now patented, Pat. No. US 5866404		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-32645P	19961210 (60)
	US 1995-8250P	19951206 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Degen, Nancy	
LEGAL REPRESENTATIVE:	Morgan & Finnegan, L.L.P., Moroz, Eugene, Auth, Dorothy	

R.  
 NUMBER OF CLAIMS: 4  
 EXEMPLARY CLAIM: 1  
 NUMBER OF DRAWINGS: 20 Drawing Figure(s); 19 Drawing Page(s)  
 LINE COUNT: 1295

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the development of collections of a single gene locus from a collection of individuals or organisms, called genome anthologies. The invention describes several novel methods for producing collections of a gene or gene families from multiple individuals or organisms. One method is targeted in vivo cloning. Another method is locus specific primer extension and exonuclease degradation method.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 22 OF 47 USPATFULL

ACCESSION NUMBER: 1999:15760 USPATFULL  
 TITLE: Yeast-bacteria shuttle vector  
 INVENTOR(S): Bradshaw, M. Suzanne, Cincinnati, OH, United States  
 Bollekens, Jacques A., Brussels, Belgium  
 Ruddie, Frank H., New Haven, CT, United States  
 PATENT ASSIGNEE(S): Yale University, New Haven, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5866404		19990202
APPLICATION INFO.:	US 1996-761704		19961206 (8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-8250P	19951206 (60)

DOCUMENT TYPE: Utility  
FILE SEGMENT: Granted  
PRIMARY EXAMINER: Railey, II, Johnny F.  
LEGAL REPRESENTATIVE: Morgan & Finnegan, L.L.P.  
NUMBER OF CLAIMS: 13  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 5 Drawing Page(s)  
LINE COUNT: 850  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The functional analysis of genes frequently requires the manipulation of

large genomic regions. A yeast-bacteria shuttle vector is described, that can be used to clone large regions of DNA by homologous recombination. The important feature of present invention is the presence of the a bacterial replication origin, which allows large DNA insert capacity. The utility of this vector lies in its ability to isolate, manipulate and maintain large fragments in bacteria and yeast, allowing for mutagenesis by yeast genetics and simplified preparation

of

plasmid DNA in bacteria.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 23 OF 47 MEDLINE

ACCESSION NUMBER: 1999240772 MEDLINE

DOCUMENT NUMBER: 99240772 PubMed ID: 10224145

TITLE: Smad1 interacts with homeobox DNA-binding proteins in bone morphogenetic protein signaling.

AUTHOR: Shi X; Yang X; Chen D; Chang Z; Cao X

CORPORATE SOURCE: Department of Pathology, University of Alabama School of Medicine, Birmingham, Alabama 35294, USA.

CONTRACT NUMBER: DK53757 (NIDDK)

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 May 7) 274 (19) 13711-7.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199906

ENTRY DATE: Entered STN: 19990614

Last Updated on STN: 19990614

Entered Medline: 19990603

AB Bone morphogenetic proteins (BMP) transduce their signals into the cell through a family of mediator proteins known as Smads. Upon phosphorylation

by the BMP receptors, Smad1 interacts with Smad4 and translocates into the

nucleus where the complex recruits DNA-binding protein(s) to activate specific gene transcription. However, the DNA-binding protein(s) involved in BMP signaling has not been identified. Using a yeast two-hybrid approach, we found that Smad1 interacts with **Hoxc-8**, a homeodomain transcription factor. The interaction between Smad1 and **Hoxc-8** was confirmed by a "pull-down" assay and a co-immunoprecipitation experiment in COS-1 cells. Interestingly, purified Smad1 inhibited **Hoxc-8** binding to the osteopontin **Hoxc-8** site in a concentration-dependent manner.

Transient transfection studies showed that native osteopontin promoter activity was elevated upon BMP stimulation. Consistent with the gel shift assay, overexpression of **Hoxc-8** abolished the BMP stimulation. When a wild type or mutant **Hoxc-8** binding element was linked to an SV40 promoter-driven reporter gene, the wild

type

but not the mutant **Hoxc-8** binding site responded to BMP stimulation. Again, overexpression of **Hoxc-8** suppressed the BMP-induced activity of the wild type reporter construct.

Our findings suggest that Smad1 interaction with **Hoxc-8** dislodges **Hoxc-8** from its DNA binding element, resulting in the induction of gene expression.

L2 ANSWER 24 OF 47 MEDLINE

ACCESSION NUMBER: 1999436250 MEDLINE  
DOCUMENT NUMBER: 99436250 PubMed ID: 10504454  
TITLE: Regulation of epidermal bullous pemphigoid antigen 1 (BPAG1) synthesis by homeoprotein transcription factors.  
AUTHOR: Mainguy G; Erno H; Montesinos M L; Lesaffre B; Wurst W; Volovitch M; Prochiantz A  
CORPORATE SOURCE: CNRS, UMR 8542, Ecole Normale Supérieure, Paris, France.  
SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1999 Oct) 113 (4) 643-50.  
Journal code: 0426720. ISSN: 0022-202X.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199911  
ENTRY DATE: Entered STN: 20000111  
Last Updated on STN: 20000111  
Entered Medline: 19991104

AB In a recent gene-trap screen, we identified the gene coding for Epidermal Bullous Pemphigoid Antigen 1 (BPAG1) as a putative transcriptional target of Engrailed and of other homeoproteins with a glutamine in position 50

of their homeodomain. We now show that the nuclear addressing of the homeodomains of Engrailed (EnHD) and Antennapedia (AntpHD) upregulates BPAG1 transcription in immortalized human keratinocytes (GMA24FIA) expressing En1. This upregulation is not observed with AntpHD-Q50A, a variant of AntpHD in which a single mutation abolishes its high-affinity binding to target DNA, thus strongly suggesting that BPAG1 upregulation homeodomains reflects their specific recognition of homeoprotein-binding sites in the BPAG1 locus. This is further confirmed by DNase I footprinting and electrophoretic mobility shift assays that reveal, within the cloned BPAG1 promoter, several sites of direct interaction with EnHD and Engrailed. Co-transfection experiments in GMA24FIA human keratinocytes, COS-7 simian fibroblasts, and CHP-100 human neuroepithelial cells show that Engrailed, Hoxa-5, and **Hoxc-8** regulate BPAG1 promoter activity and that this regulation is context-dependent. Finally, using a mouse line with LacZ inserted within the En1 locus, we identify the keratinocytes of the ventral paws, including the epithelial cells of the eccrine tubules, as a strong site of En1 expression throughout adulthood. We therefore propose that BPAG1, a 230 kDa keratin-binding protein expressed in keratinocytes and participating in the maintenance of hemidesmosomes at the dermis-epidermis border, is directly regulated by homeoprotein transcription factors.

L2 ANSWER 25 OF 47 MEDLINE

ACCESSION NUMBER: 2000099675 MEDLINE  
DOCUMENT NUMBER: 20099675 PubMed ID: 10633858  
TITLE: Regulation of a muscle-specific transgene by persistent expression of Hox genes in postnatal murine limb muscle.  
AUTHOR: Houghton L; Rosenthal N  
CORPORATE SOURCE: Cardiovascular Research Center, Massachusetts General Hospital-East, Charlestown 02129, USA.  
CONTRACT NUMBER: R01AR41926 (NIAMS)  
SOURCE: DEVELOPMENTAL DYNAMICS, (1999 Dec) 216 (4-5) 385-97.  
Journal code: 9201927. ISSN: 1058-8388.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200002  
ENTRY DATE: Entered STN: 20000309  
Last Updated on STN: 20020212  
Entered Medline: 20000222

AB Homeobox genes are necessary for the generation of the embryonic body plan

in both invertebrate and vertebrate organisms. To investigate the potential function of homeodomain proteins in normal and regenerating skeletal muscle, we analyzed patterns of clustered homeobox gene expression in neonatal and adult muscle tissue. Transcripts encoding 5' genes in the HoxA cluster were detected in muscles from both the fore- and hindlimbs of neonatal and adult mice, whereas expression of HoxC gene transcripts was generally restricted to the muscles of the hindlimb. In contrast, transcripts encoding genes of the HoxB or HoxD clusters were not detected in muscles from either fore- or hindlimbs. Although ectopic expression of select HOX proteins in muscle cell cultures had modest effects upon the activity of a co-transfected myosin light chain (MLC) enhancer, mutation of a Hox binding site in this enhancer elicited increased linked reporter gene expression. Induction of muscle damage and regeneration was accompanied by the down-regulation of at least one Hox gene, concurrent with the activation of the regenerative program. Moreover, targeted ablation of the **Hoxc-8** gene, normally expressed in mature fore- and hindlimb muscles, resulted in reduced expression of an MLC enhancer-driven transgene only in specific leg muscles. These results indicate that members of the HoxA and C clusters may, in combination, mediate various aspects of differentiation and patterning in adult musculature.

L2 ANSWER 26 OF 47 MEDLINE

ACCESSION NUMBER: 2000099671 MEDLINE  
DOCUMENT NUMBER: 20099671 PubMed ID: 10633854  
TITLE: Stage-specific homeotic vertebral transformations in mouse fetuses induced by maternal hyperthermia during somitogenesis.  
AUTHOR: Li Z L; Shiota K  
CORPORATE SOURCE: Department of Anatomy and Developmental Biology, Graduate School of Medicine, Kyoto University, Japan.  
SOURCE: DEVELOPMENTAL DYNAMICS, (1999 Dec) 216 (4-5) 336-48.  
Journal code: 9201927. ISSN: 1058-8388.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200002  
ENTRY DATE: Entered STN: 20000309  
Last Updated on STN: 20000309  
Entered Medline: 20000222

AB To investigate the heat shock effects upon somitogenesis and specification

of the vertebral identity, pregnant ICR mice were briefly exposed to 42 degrees C or 43 degrees C at E7.5, E8.5, or E9.5 (noon of the plug day = E0.5). Heat treatment induced embryonic day-specific vertebral transformations whose frequency and severity were dependent on the temperature elevation. Following a heat treatment at E8.5, the vertebral identity of T6 through S1 was shifted anteriorly by one or two segments (posterior transformations). Such shifts were found in more than one-third

of the fetuses heat-stressed at 42 degrees C, and in over 90% of those exposed to 43 degrees C. When heated at E7.5, the anterior boundary of vertebral transformations was shifted cranially to cervical levels (C1-C7), and when heated at E9.5, it was shifted caudally to the lower thoracic and lumbar levels (T13-L4). Examination of Hox gene expression domains by in situ hybridization showed that the anterior boundaries of Hoxa-5, Hoxa-7, **Hoxc-8**, and Hoxc-9 expression domains

in the paraxial mesoderm were shifted cranially by one somite segment in embryos heated at E7.5, as compared with the corresponding levels of

their

expression in control embryos. Such cranial shifts were found for *Hoxa-7*, *Hoxc-8* and *Hoxc-9*, but not for *Hoxa-5*, in embryos heated at E8.0. In embryos heated at E8.5, only the expression domains for *Hoxc-8* and *Hoxc-9* were found to be shifted. The observed stage-specific vertebral transformations and shifts of the Hox gene expression domains were consistent with the temporal colinearity and posterior predominance of Hox gene expression during development. Further histological and cytochemical analyses revealed that heat-induced vertebral transformations may not be a result of induced cell death, but heat-induced transient arrest of cell proliferation and somitogenesis could result in altered expression of Hox genes and subsequently produce vertebral transformations.

L2 ANSWER 27 OF 47 MEDLINE

ACCESSION NUMBER: 1999118342 MEDLINE

DOCUMENT NUMBER: 99118342 PubMed ID: 9919689

TITLE: Hematopoietic progenitor cell abnormalities in *Hoxc-8* null mutant mice.

AUTHOR: Shimamoto T; Tang Y; Naot Y; Nardi M; Brulet P; Bieberich C

J; Takeshita K

CORPORATE SOURCE: Department of Medicine, New York University Medical Center,

New York 10016, USA.

CONTRACT NUMBER: R01DK45118 (NIDDK)

R01HD27943 (NICHD)

T32HC07698 (NHLBI)

+

SOURCE: JOURNAL OF EXPERIMENTAL ZOOLOGY, (1999 Feb 1) 283 (2) 186-93.

Journal code: 0375365. ISSN: 0022-104X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199902

ENTRY DATE: Entered STN: 19990301

Last Updated on STN: 19990301

Entered Medline: 19990212

AB The mammalian Hox genes encode a family of conserved transcription factors

that control the establishment of the body plan during embryogenesis.

Many

Hox genes are also known to be expressed in hematopoietic cells. We found that *Hoxc-8*, a member of the Hox C cluster, is expressed in the mouse hematopoietic organs, fetal liver and adult bone marrow. To determine the role of *Hoxc-8* gene in hematopoiesis, we compared progenitor cell numbers in the fetal liver and adult bone marrow cells. We observed a significant reduction in the

number

of erythroid burst-forming unit (BFU-E) and in granulocyte/macrophage colony-forming unit (CFU-GM) in the *Hoxc-8* null mice, although the peripheral blood cell counts were normal. The hematopoietic cells from the homozygote animals exhibited normal expansion capability

in

a liquid culture system, suggesting that the decreased number of progenitor cells may be due to a defect extrinsic to the hematopoietic cells, such as in the interaction with the microenvironment.

L2 ANSWER 28 OF 47 MEDLINE

ACCESSION NUMBER: 1999259637 MEDLINE

DOCUMENT NUMBER: 99259637 PubMed ID: 10327653

TITLE: Phylogenetically conserved CK-II phosphorylation site of

the murine homeodomain protein Hoxb-6.  
 AUTHOR: Fienberg A A; Nordstedt C; Belting H G; Czernik A J; Nairn A C; Gandy S; Greengard P; Ruddle F H  
 CORPORATE SOURCE: Department of Genetics, Yale University School of Medicine,  
 Yale University, New Haven, Connecticut 06510, USA..  
 fienba@rockvax.rockefeller.edu  
 CONTRACT NUMBER: AG09464 C (NIA)  
 GM09966 (NIGMS)  
 SOURCE: JOURNAL OF EXPERIMENTAL ZOOLOGY, (1999 Apr 15) 285 (1) 76-84.  
 Journal code: 0375365. ISSN: 0022-104X.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199906  
 ENTRY DATE: Entered STN: 19990714  
 Last Updated on STN: 20020420  
 Entered Medline: 19990629

AB In an effort to characterize the signal transduction mechanisms that operate to regulate homeodomain protein function, we have analyzed the phosphorylation state of two homeodomain proteins, Hoxb-6 and **Hoxc-8**, in vitro and in vivo. The baculovirus expression system was employed to demonstrate that Hoxb-6 is phosphorylated in Sf9 cells while **Hoxc-8** is not. Using two-dimensional tryptic phosphopeptide mapping and purified protein kinases, we demonstrate that Hoxb-6 is phosphorylated in vitro by casein kinase II and cAMP-dependent protein kinase. The casein kinase II phosphorylation site was mapped to serine-214. Two-dimensional tryptic phosphopeptide mapping of immunoprecipitated Hoxb-6 from mouse embryonic spinal cords demonstrates that the same peptide phosphorylated in vitro and in Sf9 cells by casein kinase II is also phosphorylated in vivo. The conservation of this site in several homeodomain proteins from various species is discussed.

L2 ANSWER 29 OF 47 USPATFULL

ACCESSION NUMBER: 1998:151078 USPATFULL  
 TITLE: Vertebrate embryonic pattern-inducing proteins, and uses related thereto  
 INVENTOR(S): Ingham, Philip W., Summertown, England  
 McMahon, Andrew P., Lexington, MA, United States  
 Tabin, Clifford J., Cambridge, MA, United States  
 PATENT ASSIGNEE(S): President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5844079		19981201
APPLICATION INFO.:	US 1994-356060		19941214 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1993-176427, filed on 30 Dec 1993		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Walsh, Stephen		
ASSISTANT EXAMINER:	Sorensen, Kenneth H.		
LEGAL REPRESENTATIVE:	Vincent, Matthew P., Arnold, Beth E.Foley, Hoag & Eliot		
	LLP		
NUMBER OF CLAIMS:	41		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	22 Drawing Figure(s); 21 Drawing Page(s)		
LINE COUNT:	7618		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention concerns the discovery that proteins encoded by a family of vertebrate genes, termed here hedgehog-related genes, comprise

morphogenic signals produced by embryonic patterning centers, and are involved in the formation of ordered spatial arrangements of differentiated tissues in vertebrates. The present invention makes available compositions and methods that can be utilized, for example to generate and/or maintain an array of different vertebrate tissue both in vitro and in vivo.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 30 OF 47 MEDLINE  
ACCESSION NUMBER: 1998374287 MEDLINE  
DOCUMENT NUMBER: 98374287 PubMed ID: 9707582  
TITLE: Evidence for regulation of cartilage differentiation by the homeobox gene **Hoxc-8**.  
AUTHOR: Yueh Y G; Gardner D P; Kappen C  
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Samuel C. Johnson Medical Research Center, Mayo Clinic Scottsdale, 13400 East Shea Boulevard, Scottsdale, AZ 85259, USA.  
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Aug 18) 95 (17) 9956-61. Journal code: 7505876. ISSN: 0027-8424.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199809  
ENTRY DATE: Entered STN: 19980925  
Last Updated on STN: 19980925  
Entered Medline: 19980917  
AB Homeobox genes of the Hox class are required for proper patterning of skeletal elements, but how they regulate the differentiation of specific tissues is unclear. We show here that overexpression of a **Hoxc-8** transgene causes cartilage defects whose severity depends on transgene dosage. The abnormal cartilage is characterized by an accumulation of proliferating chondrocytes and reduced maturation. Since **Hoxc-8** is normally expressed in chondrocytes, these results suggest that **Hoxc-8** continues to regulate skeletal development well beyond pattern formation in a tissue-specific manner, presumably by controlling the progression of cells along the chondrocyte differentiation pathway. The comparison to Hoxd-4 and Isl-1 indicates that this role in chondrogenesis is specific to proteins of the Hox class. Their capacity for regulation of cartilage differentiation suggests that Hox genes could also be involved in human chondrodysplasias or other cartilage disorders.

L2 ANSWER 31 OF 47 MEDLINE  
ACCESSION NUMBER: 1998151516 MEDLINE  
DOCUMENT NUMBER: 98151516 PubMed ID: 9482889  
TITLE: Modification of expression and cis-regulation of Hoxc8 in the evolution of diverged axial morphology.  
AUTHOR: Belting H G; Shashikant C S; Ruddle F H  
CORPORATE SOURCE: Department of Molecular, Cellular, and Developmental Biology, Yale University, POB 208103, New Haven, CT 06520, USA.  
CONTRACT NUMBER: GM09966 (NIGMS)  
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Mar 3) 95 (5) 2355-60. Journal code: 7505876. ISSN: 0027-8424.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: GENBANK-AJ223359

ENTRY MONTH: 199804  
ENTRY DATE: Entered STN: 19980416  
Last Updated on STN: 19980416  
Entered Medline: 19980409

AB Differential Hox gene expression between vertebrate species has been implicated in the divergence of axial morphology. To examine this relationship, we have compared expression and transcriptional regulation of Hoxc8 in chicken and mouse. In both species, expression of Hoxc8 in the paraxial mesoderm and neural tube is associated with midthoracic and brachial identities, respectively. During embryogenesis, there is a temporal delay in the activation of Hoxc8 in chicken compared with mouse. As a result, chicken Hoxc8 expression in the paraxial mesoderm is at a posterior axial level, extending over a smaller domain compared with mouse Hoxc8 expression. This finding is consistent with a shorter thoracic region in chicken compared with mouse. In addition, the chicken Hoxc8 early enhancer, differing from its mouse counterpart in only a few specific nucleotides, directs a reporter gene expression to a more posterior domain in transgenic mouse embryos. These findings are consistent with the concept that the diversification of axial morphology has been achieved through changes in cis-regulation of developmental control genes.

L2 ANSWER 32 OF 47 MEDLINE

ACCESSION NUMBER: 1998130557 MEDLINE

DOCUMENT NUMBER: 98130557 PubMed ID: 9463344

TITLE: The control of rostrocaudal pattern in the developing spinal cord: specification of motor neuron subtype identity

is initiated by signals from paraxial mesoderm.

AUTHOR: Ensini M; Tsuchida T N; Belting H G; Jessell T M

CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Biochemistry

and Molecular Biophysics, Columbia University, New York, NY 10025, USA.

CONTRACT NUMBER: 5T32GM07367 (NIGMS)  
GM09966 (NIGMS)

SOURCE: DEVELOPMENT, (1998 Mar) 125 (6) 969-82.  
Journal code: 8701744. ISSN: 0950-1991.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199805

ENTRY DATE: Entered STN: 19980514  
Last Updated on STN: 19980514  
Entered Medline: 19980501

AB The generation of distinct classes of motor neurons is an early step in the control of vertebrate motor behavior. To study the interactions that control the generation of motor neuron subclasses in the developing avian spinal cord we performed in vivo grafting studies in which either the neural tube or flanking mesoderm were displaced between thoracic and brachial levels. The positional identity of neural tube cells and motor neuron subtype identity was assessed by Hox and LIM homeodomain protein expression. Our results show that the rostrocaudal identity of neural cells is plastic at the time of neural tube closure and is sensitive to positionally restricted signals from the paraxial mesoderm. Such paraxial mesodermal signals appear to control the rostrocaudal identity of neural tube cells and the columnar subtype identity of motor neurons. These results suggest that the generation of motor neuron subtypes in the developing spinal cord involves the integration of distinct rostrocaudal and dorsoventral patterning signals that derive, respectively, from paraxial and axial mesodermal cell groups.



L2 ANSWER 33 OF 47 MEDLINE  
 ACCESSION NUMBER: 1998146206 MEDLINE  
 DOCUMENT NUMBER: 98146206 PubMed ID: 9486801  
 TITLE: Increased apoptosis of motoneurons and altered somatotopic maps in the brachial spinal cord of **Hoxc-8**-deficient mice.  
 AUTHOR: Tiret L; Le Mouellic H; Maury M; Brulet P  
 CORPORATE SOURCE: Unite d'Embryologie Moleculaire, Institut Pasteur, URA 1947  
 SOURCE: du CNRS, Paris, France.  
 DEVELOPMENT, (1998 Jan) 125 (2) 279-91.  
 Journal code: 8701744. ISSN: 0950-1991.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199803  
 ENTRY DATE: Entered STN: 19980319  
 Last Updated on STN: 19980319  
 Entered Medline: 19980312

AB Mice deficient for the homeotic gene **Hoxc-8** suffer from a congenital prehension deficiency of the forepaw. During embryogenesis, **Hoxc-8** is highly expressed in motoneurons within spinal cord segments C7 to T1. These motoneurons innervate forelimb distal muscles that move the forepaw. In **Hoxc-8** mutant embryos, formation of these muscles is normal, but their innervation is perturbed. From E13.5 onwards, distal muscles normally supplied by C(7-8) MNs also receive ectopic projections from C(5-6) and T1 motoneurons. Coordinates of motor pools are altered along the rostrocaudal and also the mediolateral axes. Following this aberrant connectivity pattern and during the time of naturally occurring cell death, apoptosis is specifically enhanced in C7-T1 motoneurons. Loss of Hox-encoded regional specifications subsequently leads to a numerical deficit of motoneurons and an irreversible disorganization of motor pools.  
 In **Hoxc-8** null mutants, C(7-8) motoneurons lose their selective advantage in growth cone pathfinding behavior and/or target recognition, two essential steps in the establishment and maintenance of a functional nervous system.

L2 ANSWER 34 OF 47 MEDLINE  
 ACCESSION NUMBER: 97345900 MEDLINE  
 DOCUMENT NUMBER: 97345900 PubMed ID: 9202392  
 TITLE: Changing intestinal connective tissue interactions alters homeobox gene expression in epithelial cells.  
 AUTHOR: Duluc I; Lorentz O; Fritsch C; Leberquier C; Kedinger M; Freund J N  
 CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, Unite 381, Strasbourg, France.  
 SOURCE: JOURNAL OF CELL SCIENCE, (1997 Jun) 110 ( Pt 11) 1317-24.  
 Journal code: 0052457. ISSN: 0021-9533.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199709  
 ENTRY DATE: Entered STN: 19971013  
 Last Updated on STN: 19971013  
 Entered Medline: 19970929

AB In segmented organs, homeobox genes are involved in axial patterning and cell identity. Much less is known about their role in non-segmented endoderm derivatives such as the digestive epithelium. Using a xenograft model of fetal intestinal anlagen implanted under the skin of nude mice, we have investigated whether the expression of five homeobox genes

(HoxA-4, HoxA-9, **HoxC-8**, Cdx-1 and Cdx-2) is modified when intestinal epithelium undergoes normal development or displays heterodifferentiation in association with heterotopic mesenchyme. In homotypic associations of fetal endoderm and mesenchyme that recapitulate normal development, the overall pattern of homeobox gene expression was maintained: HoxA-9 and **HoxC-8** were the highest in the colon and ileum, respectively, and HoxA-4 was expressed all along the intestine; Cdx-1 and Cdx-2 exhibited an increasing gradient of expression from small intestine to colon. Yet, grafting per se caused a faint upregulation of HoxA-9 and **HoxC-8** in small intestinal regions in which these genes are not normally expressed, while the endoderm-mesenchyme dissociation-association step provoked a decay of Cdx-1 in the colon. In heterotopic associations of colonic endoderm with small intestinal mesenchyme, the colonic epithelium exhibited heterodifferentiation to a small intestinal-like phenotype. In this case, we observed a decay of HoxA-9 expression and an upregulation of **HoxC-8**. Additionally, heterodifferentiation of the colonic epithelium was accompanied by a downregulation of Cdx-1 and Cdx-2 to a level similar to that found in the normal small intestine. To demonstrate that mesenchyme-derived cells can influence Cdx-1 and Cdx-2 expression in the bowel epithelium, fetal jejunal endoderm was associated with intestinal fibroblastic cell lines that either support small intestinal-like or colonic-like morphogenesis. A lower expression of both homeobox genes was shown in grafts presenting the small intestinal phenotype than in those showing glandular colonic-like differentiation. Taken together, these results suggest that homeobox genes participate in the control of the positional information and/or cell differentiation in the intestinal epithelium. They also indicate that the level of Cdx-1 and Cdx-2 homeobox gene expression is influenced by epithelial-mesenchymal cell interactions in the intestinal mucosa.

L2 ANSWER 35 OF 47 MEDLINE  
 ACCESSION NUMBER: 1998071502 MEDLINE  
 DOCUMENT NUMBER: 98071502 PubMed ID: 9407586  
 TITLE: Heat shock-induced homeotic transformations of the axial skeleton and associated shifts of Hox gene expression domains in mouse embryos.  
 AUTHOR: Li Z L; Chisaka O; Koseki H; Akasaka T; Ishibashi M; Shiota  
 K  
 CORPORATE SOURCE: Department of Anatomy and Developmental Biology, Kyoto

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SOURCE: REPRODUCTIVE TOXICOLOGY, (1997 Nov-Dec) 11 (6) 761-70.  
 Journal code: 8803591. ISSN: 0890-6238.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199801  
 ENTRY DATE: Entered STN: 19980206  
 Last Updated on STN: 19980206  
 Entered Medline: 19980129

AB Pregnant ICR mice were

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transformations in more than one-third of the living fetuses, in which the morphologic identity of vertebrae (T6-S1) was shifted anteriorly by one or two segmental levels. The frequency of fetuses with vertebral transformations and the degree of the shift of vertebral identity were dependent on the length of heat exposure. The expression domains of Hoxa-7, **Hoxc-8**, and Hoxc-9 genes as examined by whole mount in situ hybridization were found to be shifted anteriorly in heated

embryos. The heat-induced shifts of Hox gene expression domains were consistent with the observed vertebral transformations and suggested

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establishment of Hox codes and subsequently, perturb the specification of vertebral identity.

L2 ANSWER 36 OF 47 MEDLINE

ACCESSION NUMBER: 1998049321 MEDLINE

DOCUMENT NUMBER: 98049321 PubMed ID: 9389453

TITLE: CHOXC-8 and CHOXD-13 expression in embryonic chick skin and

cutaneous appendage specification.

AUTHOR: Kanzler B; Prin F; Thelu J; Dhouailly D

CORPORATE SOURCE: Biologie de la Differentiation Epitheliale-UMR CNRS 5538, Institut Albert Bonniot, Universite Joseph Fourier, Grenoble, France.

SOURCE: DEVELOPMENTAL DYNAMICS, (1997 Nov) 210 (3) 274-87. Journal code: 9201927. ISSN: 1058-8388.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199802

ENTRY DATE: Entered STN: 19980224

Last Updated on STN: 19980224

Entered Medline: 19980210

AB We studied the expression of two distantly clustered Hox genes which could, respectively, be involved in specification of dorsal feather- and foot scale-forming skin in the chick embryo: cHoxc-8, a median paralog, and cHoxd-13, located at the 5' extremity of the HoxD cluster. The

cHoxc-8

transcripts are present at embryonic day 3.5 (E3.5) in the somitic cells, which give rise to the dorsal dermis by E5, and at E6.5-8.5 in the dorsal dermal and epidermal cells during the first stages of feather morphogenesis. The cHoxd-13 transcripts are present at E4.5-9.5 in the autopodial mesenchyme and at E10.5-12.5 in the plantar dermis during the initiation of reticulate scale morphogenesis. Both the cHoxc-8 and cHoxd-13 transcripts are no longer detectable after the anlagen stage of cutaneous appendage morphogenesis. Furthermore, heterotopic dermal-epidermal recombinations of dorsal, plantar, and apteric tissues revealed that the epidermal ability or inability to form feathers is already established by the time of skin formation. Retinoic acid (RA) treatment at E11 induces after 12 hr an inhibition of cHoxd-13 expression in the plantar dermis, followed by the formation of feather filaments on the reticulate scales. When E7.5 dorsal explants are treated with RA for

6

days, they form scale-like structures where the Hox transcripts are no more detectable. Protein analysis revealed that the plantar filaments, made up of feather beta-keratins, corresponded to a homeotic transformation, whereas the scale-like structures, composed also of feather beta-keratins, were teratoid. These results strengthen the hypothesis that different homeobox genes play a significant role in specifying the regional identity of the different epidermal territories.

L2 ANSWER 37 OF 47 MEDLINE

ACCESSION NUMBER: 96382518 MEDLINE

DOCUMENT NUMBER: 96382518 PubMed ID: 8790382

TITLE: Functional specificity of Hoxa-4 in vertebral patterning lies outside of the homeodomain.

AUTHOR: Sreenath T L; Pollock R A; Bieberich C J

CORPORATE SOURCE: Department of Virology, Jerome H. Holland Laboratory, Rockville, MD 20855, USA.

CONTRACT NUMBER: HD27943 (NICHD)

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Sep 3) 93 (18) 9636-40.

Journal code: 7505876. ISSN: 0027-8424.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199610  
ENTRY DATE: Entered STN: 19961106  
Last Updated on STN: 19961106  
Entered Medline: 19961024

AB The Hox family of proteins plays a central role in establishing the body plan of a wide range of metazoan organisms. Each member of this family of transcriptional regulators has a distinct functional specificity, yet they bind to similar DNA target sequences through their conserved homeodomain. The mechanisms whereby Hox proteins achieve their diverse specificities in vivo remain undefined. Using the opposing effects of Hoxa-4 and **Hoxc-8** in vertebral patterning, we demonstrate by replacing the homeodomain of Hoxa-4 with that of **Hoxc-8** that the functional specificity of Hoxa-4 does not track with the homeodomain. These observations provide evidence that other regions of Hox proteins play an important role in mediating functional specificity during mammalian embryogenesis.

L2 ANSWER 38 OF 47 MEDLINE  
ACCESSION NUMBER: 97057876 MEDLINE  
DOCUMENT NUMBER: 97057876 PubMed ID: 8902206  
TITLE: An androgen-regulated homeobox gene expressed in rat testis

and epididymis.  
AUTHOR: Lindsey J S; Wilkinson M F  
CORPORATE SOURCE: Molecular Microbiology and Immunology Graduate Program, Oregon Health Sciences University, Portland 97201, USA.  
CONTRACT NUMBER: HD 27233 (NICHD)  
T32 EY07123 (NEI)  
SOURCE: BIOLOGY OF REPRODUCTION, (1996 Nov) 55 (5) 975-83.  
Journal code: 0207224. ISSN: 0006-3363.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199702  
ENTRY DATE: Entered STN: 19970227  
Last Updated on STN: 19970227  
Entered Medline: 19970207

AB Homeobox genes encode DNA-binding proteins that regulate the transcription of subordinate downstream genes. In this study, we show that the Pem homeobox gene is expressed and regulated in a unique manner in neonatal and adult rats. Pem gene expression was primarily confined to reproductive tissue: epididymis, testis, ovary, and placenta. In the epididymis, Pem transcripts were localized by in situ hybridization analysis to the proximal cauda region, a site where spermatozoa gain fertilization competence. Pem mRNA levels dramatically increased between Days 21 and 26 postpartum in the epididymis, coincident with the induction of genes known to be responsive to testosterone (T), but in contrast to that of other genes examined, including the **Hoxc-8** homeobox gene. Pem expression was shown to be T-dependent on the basis of an absence of Pem transcripts in the epididymides of hypophysectomized rats and restoration of normal Pem mRNA levels after administration of T. In the testis, Pem mRNA levels were elevated earlier (between Days 12 and 15 postpartum) and less dramatically than in epididymis. Pem gene expression

in the testis was depressed after hypophysectomy, but normal levels of Pem expression were not restored by T treatment under the same conditions that permitted normal Pem expression in the epididymis. To our knowledge Pem is the first reported putative transcription factor that has been demonstrated to depend on androgens for expression in the epididymis, and thus Pem is a candidate as a regulator of androgen-dependent events in this tissue.

L2 ANSWER 39 OF 47 MEDLINE  
 ACCESSION NUMBER: 97042053 MEDLINE  
 DOCUMENT NUMBER: 97042053 PubMed ID: 8887324  
 TITLE: The Polycomb-group homolog Bmi-1 is a regulator of murine Hox gene expression.  
 AUTHOR: van der Lugt N M; Alkema M; Berns A; Deschamps J  
 CORPORATE SOURCE: Division of Molecular Genetics, The Netherlands Cancer Institute, Amsterdam, The Netherlands.  
 SOURCE: MECHANISMS OF DEVELOPMENT, (1996 Aug) 58 (1-2) 153-64. Journal code: 9101218. ISSN: 0925-4773.  
 PUB. COUNTRY: Ireland  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199703  
 ENTRY DATE: Entered STN: 19970313  
 Last Updated on STN: 19970313  
 Entered Medline: 19970306

AB Drosophila homeotic genes and vertebrate Hox genes are involved in the anteroposterior organization of the developing embryo. In Drosophila, the Polycomb- and trithorax-group genes are required to maintain the homeotic genes throughout development in the repressed or activated state, respectively. The murine Bmi-1 proto-oncogene was shown to exhibit homology to the Polycomb-group gene Posterior sex combs. Mice lacking the Bmi-1 gene revealed posterior transformations along the axial skeleton, whereas transgenic mice overexpressing Bmi-1 display anterior transformations. We have analysed the expression patterns of several Hox genes by RNA in situ hybridization on serial sections of 11.5- and 12.5-day Bmi-1 null mutant embryos. Furthermore, we have analysed the expression of a **Hoxc-8/LacZ** fusion gene in younger embryos. Our analyses show that Bmi-1 is involved in the repression of a subset of Hox genes from different clusters from at least day 9.5 onwards.

We discuss the possibility that members of the murine Polycomb-group can form multimeric protein complexes of different compositions with varying affinity or specificity for different subsets of Hox genes.

L2 ANSWER 40 OF 47 MEDLINE  
 ACCESSION NUMBER: 97036845 MEDLINE  
 DOCUMENT NUMBER: 97036845 PubMed ID: 8882492  
 TITLE: Target gene identification: target specific transcriptional activation by three murine homeodomain/VP16 hybrid proteins in *Saccharomyces cerevisiae*.  
 AUTHOR: Friedman-Einat M; Einat P; Snyder M; Ruddle F  
 CORPORATE SOURCE: Department of Biology, Yale University, New Haven, Connecticut 06511, USA.  
 CONTRACT NUMBER: GM09966 (NIGMS)  
 SOURCE: JOURNAL OF EXPERIMENTAL ZOOLOGY, (1996 Feb 15) 274 (3) 145-56. Journal code: 0375365. ISSN: 0022-104X.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English

FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199612  
ENTRY DATE: Entered STN: 19970128  
Last Updated on STN: 19970128  
Entered Medline: 19961211

AB The mammalian homeodomain proteins encoded by Hox genes play an important role in embryonic development by providing positional queues which define developmental identities along the anteroposterior axis of developing organisms. These proteins bind DNA specifically through their homeodomain to sequences containing ATTA cores, and thereby are thought to exert their

effect regulating downstream genes. Little is known about the specificity of binding of homeodomain proteins to their sequences and the identity of their target genes. We have developed a transcriptional activation assay in yeast which employs a homeobox/VP16 fusion gene as a transcriptional activator and a target construct in which test fragments of DNA are inserted upstream to a reporter gene. Using this assay, we compared transcriptional activation by three chimeric proteins containing the homeodomains of the mouse homeobox genes, Hoxa-5, Hoxb-6, and **Hoxc-8**. When tested on previously defined target sequences, strong differential specificities of activation were observed. In an effort to identify enhancers that normally respond to homeodomain transcriptional activators, random fragments of mouse genomic DNA were cloned upstream of the reporter gene. Genomic DNA fragments with distinct activation profiles

were obtained and were found to share matches beyond the ATTA core with previously described enhancers. These results demonstrate that the transcriptional activation system in yeast can be used as a convenient system to detect DNA motifs which bind homeodomain proteins, and subsequently, to identify authentic target genes responsive to Hox gene proteins.

L2 ANSWER 41 OF 47 MEDLINE

ACCESSION NUMBER: 96165735 MEDLINE  
DOCUMENT NUMBER: 96165735 PubMed ID: 8589738  
TITLE: Spatial and temporal regulation of a lacZ reporter transgene in a binary transgenic mouse system.  
AUTHOR: Gardner D P; Byrne G W; Ruddle F H; Kappen C  
CORPORATE SOURCE: Samuel C. Johnson Medical Research Center, Mayo Clinic, Scottsdale, AZ 85259, USA.  
SOURCE: TRANSGENIC RESEARCH, (1996 Jan) 5 (1) 37-48.  
Journal code: 9209120. ISSN: 0962-8819.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199603  
ENTRY DATE: Entered STN: 19960404  
Last Updated on STN: 19960404  
Entered Medline: 19960328

AB The transgenic mouse system is a powerful tool for the study of gene function. However, when the analysis involves genes that are critical for the normal developmental process, the usefulness of transgenic mouse systems is limited (for review see Hanahan, 1989; Westphal and Gruss, 1989; Byrne et al., 1991). This is due to potential transgene interference

with development in case of ectopic or high level expression. As a result,

establishing permanent transgenic mouse lines expressing these types of genes has proven difficult. To circumvent these difficulties, a binary transgenic mouse system has been established, termed the Multiplex System (Byrne and Ruddle, 1989). This is a two-tiered gene activation system in which expression of the gene of interest occurs only in offspring carrying

transgenes encoding both components: transactivator and transresponder. Transactivator lines contain the gene encoding the VP16 protein of herpes

simplex virus. Transresponder lines harbour the gene of interest linked to the IE promoter which includes recognition sequences for the VP16 transactivator. Previously, the inducibility of a chloramphenicol acetyltransferase reporter gene in newborn offspring that carried both a transactivator and transresponder transgene (Byrne and Ruddle, 1989) has been shown. Moreover, it has been demonstrated that expression of the VP16 protein was not detrimental to development and that transactivation appeared to be tissue specific. Here, the potential of the system for theu  
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=> s l2 and smad6

L3 2 L2 AND SMAD6

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PROCESSING COMPLETED FOR L3

L4 2 DUP REM L3 (0 DUPLICATES REMOVED)

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L4 ANSWER 1 OF 2 MEDLINE  
ACCESSION NUMBER: 2002113327 MEDLINE  
DOCUMENT NUMBER: 21683518 PubMed ID: 11711531  
TITLE: A nuclear antagonistic mechanism of inhibitory Smads in transforming growth factor-beta signaling.  
AUTHOR: Bai Shuting; Cao Xu  
CORPORATE SOURCE: Department of Pathology, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama 35294, USA.  
CONTRACT NUMBER: DK 53757 (NIDDK)  
DK 57501 (NIDDK)  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Feb 8) 277 (6) 4176-82.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200203  
ENTRY DATE: Entered STN: 20020216  
Last Updated on STN: 20020307  
Entered Medline: 20020305

AB Inhibitory Smads (I-Smads), including **Smad6** and **Smad7**, were initially characterized as cytoplasmic antagonists in the transforming growth factor-beta signaling pathway. However, I-Smads are also localized in the nucleus. Previously, we have shown that **Smad6** can function as a transcriptional co-repressor. In this study, we found both **Smad6** and **Smad7** interact with histone deacetylases (HDACs). Acetylation state of core histones plays a critical role in gene transcription regulation. An HDAC inhibitor, trichostatin A, released **Smad6**-mediated transcription repression. Moreover, class I HDACs (HDAC-1 and -3), not class II HDACs (HDAC-4, -5, and -6), were co-immunoprecipitated with **Smad6**. Endogenous HDAC-1 was also shown to interact with both **Smad6** and **Hoxc-8**. Mapping of the interaction domain indicates **Smad6** MH2 domain is mainly involved in recruiting HDAC-1. Most interestingly, **Smad6** also binds to DNA through its MH1 domain, and the MH2 domain of **Smad6** masks this binding activity, indicating that **Smad6** MH1 and MH2 domains associate reciprocally and inhibit each other's function. **Hoxc-8** induces **Smad6** binding to

DNA as a transcriptional complex. Our findings revealed that I-Smads act as antagonists in the nucleus by recruiting HDACs.

AB Inhibitory Smads (I-Smads), including **Smad6** and **Smad7**, were initially characterized as cytoplasmic antagonists in the transforming growth factor-beta signaling pathway. However, I-Smads are also localized in the nucleus. Previously, we have shown that **Smad6** can function as a transcriptional co-repressor. In this study, we found both **Smad6** and **Smad7** interact with histone deacetylases (HDACs). Acetylation state of core histones plays a critical role in gene transcription regulation. An HDAC inhibitor, trichostatin A, released **Smad6**-mediated transcription repression. Moreover, class I HDACs (HDAC-1 and -3), not class II HDACs (HDAC-4, -5, and -6), were co-immunoprecipitated with **Smad6**. Endogenous HDAC-1 was also shown to interact with both **Smad6** and **Hoxc-8**. Mapping of the interaction domain indicates **Smad6** MH2 domain is mainly involved in recruiting HDAC-1. Most interestingly, **Smad6** also binds to DNA through its MH1 domain, and the MH2 domain of **Smad6** masks this binding activity, indicating that **Smad6** MH1 and MH2 domains associate reciprocally and inhibit each other's function. **Hoxc-8** induces **Smad6** binding to DNA as a transcriptional complex. Our findings revealed that I-Smads act as antagonists in the nucleus by recruiting. . . .

CN 0 (DNA Probes); 0 (DNA-Binding Proteins); 0 (Enzyme Inhibitors); 0 (Homeodomain Proteins); 0 (**Hoxc-8** protein); 0 (**Smad6** protein); 0 (**Smad7** protein); 0 (Trans-Activators); 0 (Transforming Growth Factor beta); EC 3.5.1.- (Histone Deacetylase)

L4 ANSWER 2 OF 2 MEDLINE

ACCESSION NUMBER: 2000187528 MEDLINE  
DOCUMENT NUMBER: 20187528 PubMed ID: 10722652  
TITLE: **Smad6** as a transcriptional corepressor.  
AUTHOR: Bai S; Shi X; Yang X; Cao X  
CORPORATE SOURCE: Department of Pathology, University of Alabama School of Medicine, Birmingham, Alabama 35294, USA.  
CONTRACT NUMBER: DK53757 (NIDDK)  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12) 8267-70.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200004  
ENTRY DATE: Entered STN: 20000505  
Last Updated on STN: 20000505  
Entered Medline: 20000427

AB **Smad6** and **Smad7**, a subgroup of Smad proteins, antagonize the signals elicited by transforming growth factor-beta. These two Smads, induced by transforming growth factor-beta or bone morphogenetic protein (BMP) stimulation, form stable associations with their activated type I receptors, blocking phosphorylation of receptor-regulated Smads in the cytoplasm. Here we show that **Smad6** interacts with homeobox (Hox) c-8 as a transcriptional corepressor, inhibiting BMP signaling in the nucleus. The interaction between **Smad6** and **Hoxc-8** was identified by a yeast two-hybrid approach and further demonstrated by co-immunoprecipitation assays in cells. Gel shift assays show that **Smad6**, but not **Smad7**, interacts with both **Hoxc-8** and **Hoxa-9** as a heterodimer when binding to DNA. More importantly, the **Smad6-Hoxc-8** complex inhibits interaction of **Smad1** with **Hoxc-8**- and **Smad1**-induced transcription activity. These data indicate that **Smad6** interacts with Hox transcription factors as part of the negative feedback circuit in the BMP signaling pathway.

TI **Smad6** as a transcriptional corepressor.

AB **Smad6** and **Smad7**, a subgroup of Smad proteins, antagonize the signals elicited by transforming growth factor-beta. These two Smads,



induced by. . . stable associations with their activated type I receptors, blocking phosphorylation of receptor-regulated Smads in the cytoplasm. Here we show that **Smad6** interacts with homeobox (Hox) c-8 as a transcriptional corepressor, inhibiting BMP signaling in the nucleus. The interaction between **Smad6** and **Hoxc-8** was identified by a yeast two-hybrid approach and further demonstrated by co-immunoprecipitation assays in cells. Gel shift assays show that **Smad6**, but not Smad7, interacts with both **Hoxc-8** and Hoxa-9 as a heterodimer when binding to DNA. More importantly, the **Smad6-Hoxc-8** complex inhibits interaction of Smad1 with **Hoxc-8** and Smad1-induced transcription activity. These data indicate that **Smad6** interacts with Hox transcription factors as part of the negative feedback circuit in the BMP signaling pathway.

CN 0 (Bone Morphogenetic Proteins); 0 (DNA-Binding Proteins); 0 (Homeodomain Proteins); 0 (**Hoxc-8** protein); 0 (Repressor Proteins); 0 (Sialoglycoproteins); 0 (Smad1 protein); 0 (**Smad6** protein); 0 (Trans-Activators)

=> d kwic 6-8

2 ANSWERS ARE AVAILABLE. SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE

The answer numbers requested are not in the answer set.

ENTER ANSWER NUMBER OR RANGE (1):1

L4 ANSWER 1 OF 2 MEDLINE

AB Inhibitory Smads (I-Smads), including **Smad6** and Smad7, were initially characterized as cytoplasmic antagonists in the transforming growth factor-beta signaling pathway. However, I-Smads are also localized in the nucleus. Previously, we have shown that **Smad6** can function as a transcriptional co-repressor. In this study, we found both **Smad6** and Smad7 interact with histone deacetylases (HDACs). Acetylation state of core histones plays a critical role in gene transcription regulation. An HDAC inhibitor, trichostatin A, released **Smad6**-mediated transcription repression. Moreover, class I HDACs (HDAC-1 and -3), not class II HDACs (HDAC-4, -5, and -6), were co-immunoprecipitated with **Smad6**. Endogenous HDAC-1 was also shown to interact with both **Smad6** and **Hoxc-8**. Mapping of the interaction domain indicates **Smad6** MH2 domain is mainly involved in recruiting HDAC-1. Most interestingly, **Smad6** also binds to DNA through its MH1 domain, and the MH2 domain of **Smad6** masks this binding activity, indicating that **Smad6** MH1 and MH2 domains associate reciprocally and inhibit each other's function. **Hoxc-8** induces **Smad6** binding to DNA as a transcriptional complex. Our findings revealed that I-Smads act as antagonists in the nucleus by recruiting. . .

CN 0 (DNA Probes); 0 (DNA-Binding Proteins); 0 (Enzyme Inhibitors); 0 (Homeodomain Proteins); 0 (**Hoxc-8** protein); 0 (**Smad6** protein); 0 (Smad7 protein); 0 (Trans-Activators); 0 (Transforming Growth Factor beta); EC 3.5.1.- (Histone Deacetylase)

=> d l3 kwic 6-8

2 ANSWERS ARE AVAILABLE. SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE

The answer numbers requested are not in the answer set.

ENTER ANSWER NUMBER OR RANGE (1):2

L3 ANSWER 2 OF 2 MEDLINE

TI **Smad6** as a transcriptional corepressor.

AB **Smad6** and Smad7, a subgroup of Smad proteins, antagonize the

signals elicited by transforming growth factor-beta. These two Smads, induced by. . . stable associations with their activated type I receptors, blocking phosphorylation of receptor-regulated Smads in the cytoplasm. Here we show that **Smad6** interacts with homeobox (Hox) c-8 as a transcriptional corepressor, inhibiting BMP signaling in the nucleus. The interaction between **Smad6** and **Hoxc-8** was identified by a yeast two-hybrid approach and further demonstrated by co-immunoprecipitation assays in cells. Gel shift assays show that **Smad6**, but not Smad7, interacts with both **Hoxc-8** and Hoxa-9 as a heterodimer when binding to DNA. More importantly, the **Smad6-Hoxc-8** complex inhibits interaction of Smad1 with **Hoxc-8** and Smad1-induced transcription activity. These data indicate that **Smad6** interacts with Hox transcription factors as part of the negative feedback circuit in the BMP signaling pathway.

CN 0 (Bone Morphogenetic Proteins); 0 (DNA-Binding Proteins); 0 (Homeodomain Proteins); 0 (**Hoxc-8** protein); 0 (Repressor Proteins); 0 (Sialoglycoproteins); 0 (Smad1 protein); 0 (**Smad6** protein); 0 (Trans-Activators)

=> d history

(FILE 'HOME' ENTERED AT 15:43:30 ON 01 AUG 2002)

FILE 'MEDLINE, USPATFULL' ENTERED AT 15:43:40 ON 01 AUG 2002

L1 47 S HOXC()8  
 L2 47 DUP REM L1 (0 DUPLICATES REMOVED)  
 L3 2 S L2 AND SMAD6  
 L4 2 DUP REM L3 (0 DUPLICATES REMOVED)

=> d l2 kwic 6-8

L2 ANSWER 6 OF 47 USPATFULL

DETD . . . is an apparent homeotic alteration in the gut of a transgenic mouse in which the anterior limit of expression of **Hoxc-8** is shifted rostrally: a portion of foregut epithelium mis-differentiates as midgut (Pollock and Bieberich, (1992) Cell 71:911-923).

L2 ANSWER 7 OF 47 USPATFULL

DETD . . . is an apparent homeotic alteration in the gut of a transgenic mouse in which the anterior limit of expression of **Hoxc-8** is shifted rostrally: a portion of foregut epithelium mis-differentiates as midgut (Pollock and Bieberich, (1992) Cell 71:911-923).

L2 ANSWER 8 OF 47 USPATFULL

DRWD FIGS. 4A and 4B. Southern Analysis of pClC9C6 recombination products. Filters were hybridized with a **Hoxc-8** probe. Restriction enzymes used are shown. kb: 1 kb ladder size markers (Gibco/BRL), position and size of marker bands are. . .

DETD . . . used to isolate large subregions of YACs using homologous recombination in yeast. For example, a 27 kb region containing the **Hoxc-8** gene has been cloned from a 440 kb Hoxc YAC.

Also, the entire insert of 130 kb from a Hoxb. . .

DETD . . . for targeted mutagenesis of the selected regions before transformation into bacteria. For example, the lacZ gene was inserted in

the **Hoxc-8** gene in the pClC9C6 recombinant by homologous recombination and generated .beta.-galactosidase expressing transgenic embryos that recapitulate the endogenous **Hoxc-8** expression pattern.

DETD . . . of the Hoxb and Hoxc cluster YACs have been previously

described (7, 8). The targeting vector designed to clone the **Hoxc-8** gene, pClC9C6, was made as follows. PCR primers for the Hoxc-6 gene (9) were designed to the 5' untranslated region. .

DETD . . . vectors were generated with recombinogenic ends of approximately 500 bp each (FIG. 3). The first was designed to isolate the **Hoxc-8** allele from a 440 kb YAC containing the entire Hoxc cluster (8). Recombinogenic ends were designed to be homologous to genomic regions adjacent to the two genes flanking **Hoxc-8**: Hoxc-9 and Hoxc-6. The targeting vector designed to isolate **Hoxc-8**, pClC9C6, contained PCR generated ends homologous to the 3' untranslated region of Hoxc-9 and to the 5' untranslated region of. . .

DETD . . . vector primer 5'-TTAAAGAACGTGGACTCCAACG-3' SEQ ID NO:9. Hoxc-6 primer 5'-ACTGTGCTCTGCAGTCTCATCCG-3' SEQ ID NO:10. 2) Primers specific to the second exon of **Hoxc-8**. 5' primer 5'-CGCAGCGGTCGACAAACTTACA-3' SEQ ID NO:11; 3' primer 5'-CTCCTCCTCTTTCTCCTCTTCCTA-3' SEQ ID NO:12. The primers used to detect recombinants for pClYA. . .

DETD . . . probe used for hybridization of Hoxc YAC derived DNA was a 272 bp PCR product from the second exon of **Hoxc-8**. The probe used for hybridization of Hoxb YAC derived DNA was a 250 bp PCR product from the first exon. . .

=> b registry

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	40.33	40.54

FILE 'REGISTRY' ENTERED AT 15:56:46 ON 01 AUG 2002  
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DICTIONARY FILE UPDATES: 31 JUL 2002 HIGHEST RN 441711-84-8

TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> s hoxc()8

12 HOXC  
1885035 8  
L5 1 HOXC(W)8

=> d 15

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS  
RN 117102-67-7 REGISTRY  
CN Protein (mouse clone 3.1c gene Hox-3.1 reduced) (9CI) (CA INDEX NAME)  
OTHER NAMES:  
CN Protein (mouse clone 3.1c gene Hoxc-8 reduced)

FS PROTEIN SEQUENCE  
MF Unspecified  
CI MAN  
SR CA  
LC STN Files: CA, CAPLUS

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*  
\*\*\* USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE \*\*\*  
3 REFERENCES IN FILE CA (1967 TO DATE)  
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> b biosis

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	9.96	50.50

FILE 'BIOSIS' ENTERED AT 15:57:17 ON 01 AUG 2002  
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FILE COVERS 1969 TO DATE.  
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 31 July 2002 (20020731/ED)

=> s hoxc()8

91 HOXC  
962477 8  
L6 48 HOXC(W)8

=> dup rem l6

PROCESSING COMPLETED FOR L6  
L7 48 DUP REM L6 (0 DUPLICATES REMOVED)

=> d kwic l7 1-10

L7 ANSWER 1 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AB. . . HDACs (HDAC-4, -5, and -6), were co-immunoprecipitated with Smad6. Endogenous HDAC-1 was also shown to interact with both Smad6 and **Hoxc-8**. Mapping of the interaction domain indicates Smad6 MH2 domain is mainly involved in recruiting HDAC-1. Most interestingly, Smad6 also binds. . . of Smad6 masks this binding activity, indicating that Smad6 MH1 and MH2 domains associate reciprocally

and inhibit each other's function. **Hoxc-8** induces Smad6 binding to DNA as a transcriptional complex. Our findings revealed that I-Smads act as antagonists in the nucleus. . .

L7 ANSWER 2 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AB. . . Hox complex. We found that these characteristics apply to several Hox genes expressed in developing chick skin (Hoxb-4, Hoxa-7 and **Hoxc-8**), and we classed this group of genes as regionally restricted. To our surprise, we found that most of the Hox. .

GEN chicken Hoxa-11 gene (Galliformes); chicken Hoxa-7 gene (Galliformes); chicken Hoxb-4 gene (Galliformes); chicken Hoxc-6 gene (Galliformes); chicken **Hoxc-8** gene (Galliformes); chicken Hoxd-10 gene (Galliformes); chicken Hoxd-11 gene (Galliformes); chicken Hoxd-12 gene (Galliformes); chicken Hoxd-13 gene (Galliformes); chicken Hoxd-4.

L7 ANSWER 3 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AB The present invention demonstrates that BMP-2/4 activates osteopontin gene transcription by removing **Hoxc-8** binding through Smad1 interaction with the **Hoxc-8** DNA binding domain. Since the DNA binding domain is conserved in all Hox and homeodomain-containing proteins, Smad1 likely interacts with. . .

IT Major Concepts  
 Methods and Techniques; Molecular Genetics (Biochemistry and Molecular Biophysics)

IT Chemicals & Biochemicals  
 BMP-2/4; Hox-containing proteins; **Hoxc-8** DNA binding domain; Smad-1; homeodomain-containing proteins; osteopontin

L7 ANSWER 4 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AB. . . constitutively active BMP type IA receptor ALK3 (Q233) stimulated the OPG promoter. Deletion analysis of the OPG promoter identified two **Hoxc-8** binding sites that respond to BMP stimulation. Glutathione S-transferase-**Hoxc-8** protein binds to these two Hox sites specifically. Consistent with the transfection results of the native promoter, ALK3 or Smad1 linker region, which interacts with **Hoxc-8**, stimulated the activation of the reporter construct with the two Hox sites. Overexpression of **Hoxc-8** inhibited the induced promoter activity. When the two Hox binding sites were mutated, ALK3 or Smad1 linker region no longer. . .

L7 ANSWER 5 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AB. . . to bind to a 50-base pair DNA element (-179 to -229) from the OPN promoter. Also, we found that both **Hoxc-8** and Hoxa-9 bound to a Hox binding site adjacent to Smad3 binding sequence. Interestingly, Smad4, the common partner for both. . .

L7 ANSWER 6 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AB. . . cesium chloride gradient centrifugation in the presence of ethidium bromide and 14C incorporation was determined. Methylation of a selected gene, **Hoxc-8**, was assessed by using methylation-specific restriction enzymes. The 14C activity was found superimposed over the DNA-containing fraction, indicating incorporation. DNA. . . embryos treated with 4 mg MeOH/mL CM gave the highest incorporation of 14C-MeOH (8 mg/mL was growth inhibiting). Methylation of **Hoxc-8** appeared to be increased in embryos treated with 4 mg MeOH/mL CM, but not in embryos treated with 8 mg. . .

GEN **Hoxc-8** gene

L7 ANSWER 7 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AB. . . cells by means of adenoviral infection leads to the induction of Wnt-8c and the posterior Hox genes, Hoxa-7, Hoxc-6, and **Hoxc-8**. Cardiogenesis is not inhibited in cCdx-B expressing anterior lateral mesoderm, indicating that anterior cell fates are not respecified with the. . .

L7 ANSWER 8 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 GEN chicken Hoxa-11 gene (Galliformes); chicken Hoxa-7 gene (Galliformes); chicken Hoxb-4 gene (Galliformes); chicken Hoxc-6 gene (Galliformes); chicken **Hoxc-8** gene (Galliformes); chicken Hoxd-13 gene (Galliformes); chicken Hoxd-4 gene (Galliformes)

L7 ANSWER 9 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 GEN Drosophila lethal-(2) giant larvae tumor suppressor gene (Diptera):  
 HUGL-1 human homolog, HUGL-2 human homolog, inverse **HOXC-8** gene expression correlation, tumor cell expression, tumor development role

L7 ANSWER 10 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AB. . . Smads 1 and 4 were recently demonstrated to mediate BMP activation  
of the OPN promoter by inhibiting the interaction of **Hoxc-8**  
protein with a Hox-binding element. While previous studies have  
indicated that specific DNA sequences are recognized by Smad complexes  
in.

=> s l7 and smad6

L8 48 S L7  
99 SMAD6  
L9 4 L8 AND SMAD6

=> dup rem l9

PROCESSING COMPLETED FOR L9  
L10 4 DUP REM L9 (0 DUPLICATES REMOVED)

=> d l10 ibib abs tot

L10 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 2002:185311 BIOSIS  
DOCUMENT NUMBER: PREV200200185311  
TITLE: A nuclear antagonistic mechanism of inhibitory Smads in  
transforming growth factor-beta signaling.  
AUTHOR(S): Bai, Shuting; Cao, Xu (1)  
CORPORATE SOURCE: (1) Dept. of Pathology, University of Alabama at  
Birmingham  
School of Medicine, 1670 University Blvd., VH G002,  
Birmingham, AL, 35294-0019: cao@path.uab.edu USA  
SOURCE: Journal of Biological Chemistry, (February 8, 2002) Vol.  
277, No. 6, pp. 4176-4182. <http://www.jbc.org/>. print.  
ISSN: 0021-9258.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
AB Inhibitory Smads (I-Smads), including **Smad6** and **Smad7**, were  
initially characterized as cytoplasmic antagonists in the transforming  
growth factor-beta signaling pathway. However, I-Smads are also localized  
in the nucleus. Previously, we have shown that **Smad6** can  
function as a transcriptional co-repressor. In this study, we found both  
**Smad6** and **Smad7** interact with histone deacetylases (HDACs).  
Acetylation state of core histones plays a critical role in gene  
transcription regulation. An HDAC inhibitor, trichostatin A, released  
**Smad6**-mediated transcription repression. Moreover, class I HDACs  
(HDAC-1 and -3), not class II HDACs (HDAC-4, -5, and -6), were  
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shown to interact with both **Smad6** and **Hoxc-8**.  
. Mapping of the interaction domain indicates **Smad6** MH2 domain  
is mainly involved in recruiting HDAC-1. Most interestingly, **Smad6**  
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**Smad6** masks this binding activity, indicating that **Smad6**  
MH1 and MH2 domains associate reciprocally and inhibit each other's  
function. **Hoxc-8** induces **Smad6** binding to  
DNA as a transcriptional complex. Our findings revealed that I-Smads act  
as antagonists in the nucleus by recruiting HDACs.

L10 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 2000:346677 BIOSIS  
DOCUMENT NUMBER: PREV200000346677  
TITLE: **Smad6** as a transcriptional corepressor.  
AUTHOR(S): Bai, Shuting; Shi, Xingming; Yang, Xiangli; Cao, Xu (1)  
CORPORATE SOURCE: (1) 1670 University Blvd., VH G002, Birmingham, AL,

35294-0019 USA  
SOURCE: Journal of Biological Chemistry, (March 24, 2000) Vol.  
275,

No. 12, pp. 8267-8270. print.  
ISSN: 0021-9258.

DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB **Smad6** and **Smad7**, a subgroup of **Smad** proteins, antagonize the signals elicited by transforming growth factor-beta. These two **Smads**, induced by transforming growth factor-beta or bone morphogenetic protein (BMP) stimulation, form stable associations with their activated type I receptors, blocking phosphorylation of receptor-regulated **Smads** in the cytoplasm. Here we show that **Smad6** interacts with homeobox (Hox) c-8 as a transcriptional corepressor, inhibiting BMP signaling in the nucleus. The interaction between **Smad6** and **Hoxc-8** was identified by a yeast two-hybrid approach and further demonstrated by co-immunoprecipitation assays in cells. Gel shift assays show that **Smad6**, but not **Smad7**, interacts with both **Hoxc-8** and **Hoxa-9** as a heterodimer when binding to DNA. More importantly, the **Smad6-Hoxc-8** complex inhibits interaction of **Smad1** with **Hoxc-8** and **Smad1**-induced transcription activity. These data indicate that **Smad6** interacts with Hox transcription factors as part of the negative feedback circuit in the BMP signaling pathway.

L10 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:408840 BIOSIS

DOCUMENT NUMBER: PREV200000408840

TITLE: Histone deacetylase (HDAC) mediates **Smad6** repressive function in BMP signaling pathway.

AUTHOR(S): Bai, S. (1); Cao, X. (1)

CORPORATE SOURCE: (1) Pathology, University of Alabama at Birmingham, Birmingham, AL USA

SOURCE: Journal of Bone and Mineral Research, (September, 2000) Vol. 15, No. Suppl. 1, pp. S205. print.

Meeting Info.: Twenty-Second Annual Meeting of the American

Society for Bone and Mineral Research Toronto, Ontario, Canada September 22-26, 2000 American Society for Bone and Mineral Research  
. ISSN: 0884-0431.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L10 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1999:431055 BIOSIS

DOCUMENT NUMBER: PREV199900431055

TITLE: **Smad6** interacts with **Hoxc-8**

as a transcriptional co-repressor in BMP signaling.

AUTHOR(S): Bai, Shuting (1); Shi, Xingming (1); Yang, Xiangli (1); Cao, Xu (1)

CORPORATE SOURCE: (1) Pathology, University of Alabama at Birmingham, Birmingham, AL USA

SOURCE: Journal of Bone and Mineral Research, (Sept., 1999) Vol. 14, No. SUPPL. 1, pp. S146.

Meeting Info.: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research St. Louis, Missouri, USA September 30-October 4, 1999 American Society for Bone and Mineral Research

. ISSN: 0884-0431.

DOCUMENT TYPE: Conference

LANGUAGE: English

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(c) 2002 The HW Wilson Co.  
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 2001 (c) Action Potential  
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Set	Items	Description
S1	7	HOXC8 AND SMAD?
S2	7	RD (unique items)

>>>KWIC option is not available in file(s): 41, 77, 399

**2/3,K/1 (Item 1 from file: 399)**  
 DIALOG(R)File 399:CA SEARCH(R)  
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**135353612 CA: 135(25)353612u JOURNAL**  
**Transcriptional mechanisms of bone morphogenetic protein-induced osteoprotegrin gene expression**  
 AUTHOR(S): Wan, Mei; Shi, Xingming; Feng, Xu; Cao, Xu  
 LOCATION: Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA  
 JOURNAL: J. Biol. Chem. DATE: 2001 VOLUME: 276 NUMBER: 13 PAGES: 10119-10125 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

**2/3,K/2 (Item 2 from file: 399)**  
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**135190556 CA: 135(14)190556n JOURNAL**  
**Smad interactors in bone morphogenetic protein signaling**  
 AUTHOR(S): Yang, Xiangli; Cao, Xu  
 LOCATION: Department of Pathology, University of Alabama, Birmingham, AL, USA  
 JOURNAL: Methods Mol. Biol. (Totowa, NJ, U. S.) DATE: 2001 VOLUME: 177 NUMBER: Two-Hybrid Systems PAGES: 163-178 CODEN: MMBIED ISSN: 1064-3745 LANGUAGE: English PUBLISHER: Humana Press Inc.

**2/3,K/3 (Item 3 from file: 399)**  
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**134364569 CA: 134(26)364569r DISSERTATION**  
**Bone morphogenetic proteins induce gene transcription and osteoblastic differentiation through the interaction between Smad1 and Hoxc-8**  
 AUTHOR(S): Yang, Xiangli  
 LOCATION: University of Alabama at Birmingham, USA  
 DATE: 2000 PAGES: 204 pp. CODEN: DABBBA LANGUAGE: English CITATION: Diss. Abstr. Int., B 2000, 61(3), 1234 AVAIL: UMI, Order No. DA9964660

**2/3,K/4 (Item 4 from file: 399)**  
 DIALOG(R)File 399:CA SEARCH(R)  
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134158510 CA: 134(12)158510m PATENT

**The interaction of Smad6 with Hox proteins and BMB signalling and uses thereof in regulation of bone formation**

INVENTOR(AUTHOR): Cao, Xu; Shi, Xingming; Bai, Shuting

LOCATION: USA

ASSIGNEE: Uab Research Foundation

PATENT: PCT International ; WO 0111013 A2 DATE: 20010215

APPLICATION: WO 2000US40563 (20000803) \*US PV147161 (19990804)

PAGES: 34 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-000/A

DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

2/3,K/5 (Item 5 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

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132178572 CA: 132(14)178572v JOURNAL

**Smad1 domains interacting with Hoxc-8 induce osteoblast differentiation**

AUTHOR(S): Yang, Xiangli; Ji, Xiaohui; Shi, Xingming; Cao, Xu

LOCATION: Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA

JOURNAL: J. Biol. Chem. DATE: 2000 VOLUME: 275 NUMBER: 2 PAGES:

1065-1072 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

2/3,K/6 (Item 6 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

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131098451 CA: 131(8)98451u JOURNAL

**Smad1 interacts with homeobox DNA-binding proteins in bone morphogenetic protein signaling**

AUTHOR(S): Shi, Xingming; Yang, Xiangli; Chen, Di; Chang, Zhijie; Cao, Xu

LOCATION: Department of Pathology, University of Alabama School of Medicine, Birmingham, AL, 35294, USA

JOURNAL: J. Biol. Chem. DATE: 1999 VOLUME: 274 NUMBER: 19 PAGES:

13711-13717 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

2/3,K/7 (Item 1 from file: 266)

DIALOG(R)File 266:FEDRIP

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00319803

IDENTIFYING NO.: 1R01DK57501-01A1 AGENCY CODE: CRISP

**MECHANISM OF \*SMAD1\* MEDIATED OSTEOBLAST DIFFERENTIATION**

PRINCIPAL INVESTIGATOR: CAO, XU

ADDRESS: UNIV OF ALABAMA, BIRMINGHAM 1670 UNIVERSITY BLVD, VH G001 BIRMINGHAM, AL 35294-0019

PERFORMING ORG.: UNIVERSITY OF ALABAMA AT BIRMINGHAM, BIRMINGHAM, ALABAMA

SPONSORING ORG.: NAT INST OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

FY : 2001

**MECHANISM OF \*SMAD1\* MEDIATED OSTEOBLAST DIFFERENTIATION**

...SUMMARY: superfamily, are potent growth factors in inducing osteoblast differentiation and stimulating bone formation. Signaling in TGF-beta superfamily is mediated by direct phosphorylation of \*Smad\* proteins.

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Set	Items	Description
S1	1	SMAD6 (S) HOXC8
S2	1	SMAD6 AND HOXC8
S3	5504360	HOX WITH (BIND? OR INTERACT? OR ASSOCIAT?)
S4	106	S3 AND SMAD6
S5	40	RD (unique items)
S6	6	S5 AND HOXC

>>>KWIC option is not available in file(s): 41, 77, 399

**6/3,K/1 (Item 1 from file: 5)**  
 DIALOG(R)File 5:Biosis Previews(R)  
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13556490 BIOSIS NO.: 200200185311

**A nuclear antagonistic mechanism of inhibitory Smads in transforming growth factor-beta signaling.**

AUTHOR: Bai Shuting; Cao Xu(a)

AUTHOR ADDRESS: (a)Dept. of Pathology, University of Alabama at Birmingham  
 School of Medicine, 1670 University Blvd., VH G002, Birmingham, AL,  
 35294-0019\*\*USA E-Mail: cao@path.uab.edu

JOURNAL: Journal of Biological Chemistry 277 (6):p4176-4182 February 8,  
 2002

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

**ABSTRACT:** Inhibitory Smads (I-Smads), including \*Smad6\* and Smad7, were initially characterized as cytoplasmic antagonists in the transforming growth factor-beta signaling pathway. However, I-Smads are also localized in the nucleus. Previously, we have shown that \*Smad6\* can function as a transcriptional co-repressor. In this study, we found both \*Smad6\* and Smad7 \*interact\* with histone deacetylases (HDACs). Acetylation state of core histones plays a critical role in gene transcription regulation. An HDAC inhibitor, trichostatin A, released \*Smad6\*-mediated transcription repression. Moreover, class I HDACs (HDAC-1 and -3), not class II HDACs (HDAC-4, -5, and -6), were co-immunoprecipitated with \*Smad6\*. Endogenous HDAC-1 was also shown to \*interact\* with both \*Smad6\* and \*Hoxc\*-8. Mapping of the \*interaction\* domain indicates \*Smad6\* MH2 domain is mainly involved in recruiting HDAC-1. Most interestingly, \*Smad6\* also binds to DNA through its MH1 domain, and the MH2 domain of \*Smad6\* masks this binding activity, indicating that \*Smad6\* MH1 and MH2 domains associate reciprocally and inhibit each other's function. \*Hoxc\*-8 induces \*Smad6\* binding to DNA as a transcriptional complex. Our findings revealed that I-Smads act as antagonists in the nucleus by recruiting HDACs.

**6/3,K/2 (Item 2 from file: 5)**  
 DIALOG(R)File 5:Biosis Previews(R)  
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08164078 Genuine Article#: 232CA No. References: 0

**Title: \*Smad6\* \*interacts\* with \*Hoxc\*-8 as a transcriptional go-repressor in BMP signaling.**

Author(s): Bai ST; Shi XM; Yang XL; Cao X

Corporate Source: UNIV ALABAMA, /BIRMINGHAM//AL/

Journal: JOURNAL OF BONE AND MINERAL RESEARCH, 1999, V14, 1 (SEP), P 1053-1053

ISSN: 0884-0431 Publication date: 19990900

Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148

Language: English Document Type: MEETING ABSTRACT

*Q m 117.7 65*  
*r Adonis*

**Title: \*Smad6\* \*interacts\* with \*Hoxc\*-8 as a transcriptional go-repressor in BMP signaling.**

6/3,K/5 (Item 1 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.

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0268006 DBA Accession No.: 2001-07760 PATENT

**Regulating bone formation, useful e.g. for treating osteoporosis, comprises altering the activity of \*Smad6\* protein in forming complexes with \*Hoxc\*-8 - \*Smad6\* protein and \*Hoxc\*-8 protein \*interaction\* useful for drug screening**

AUTHOR: Cao X; Shi X; Bai S

CORPORATE SOURCE: Birmingham, AL, USA.

PATENT ASSIGNEE: Univ.Alabama 2001

PATENT NUMBER: WO 200111013 PATENT DATE: 20010215 WPI ACCESSION NO.: 2001-191529 (2019)

PRIORITY APPLIC. NO.: US 147161 APPLIC. DATE: 19990804

NATIONAL APPLIC. NO.: WO 2000US40563 APPLIC. DATE: 20000803

LANGUAGE: English

**Regulating bone formation, useful e.g. for treating osteoporosis, comprises altering the activity of \*Smad6\* protein in forming complexes with \*Hoxc\*-8 - \*Smad6\* protein and \*Hoxc\*-8 protein \*interaction\* useful for drug screening**

ABSTRACT: A method for regulating bone formation is claimed. It involves a composition (A) that alters the binding activity of \*Smad6\* protein, where an increase or decrease in \*Smad6\* increases or decreases \*Smad6\*/\*Hoxc\*-8 complexes and maintains or relieves transcriptional repression of genes involved in bone formation, respectively. Also claimed are: regulating nuclear bone morphogenetic protein (BMP) signaling in an animal; screening for compounds (I) that disrupt transcriptional repression of a gene; regulating expression of gene (II) that binds \*Hoxc\*-8 by altering the level of \*Smad6\* protein where \*Smad6\* may be increased by overexpression or upregulation of its gene, and decreased by antisense hybridization of \*Smad6\* RNA; and inducing transcription of a gene (III) that encodes osteopontin, osteoprotegrin, OPGL or RANK by inhibiting \*Smad6\*. The method is used e.g. to treat osteoporosis. The \*interaction\* between \*Smad6\* and \*Hoxc\*-8 is also used as the basis for screening assays to identify compounds that disrupt transcriptional regulation of gene, to regulate expression of genes that bind \*Hoxc\*-8, and for inducing transcription of the genes for osteopontin, osteoprotegrin, OPGL or RANK. (34pp)

DESCRIPTORS: recombinant Smd6, \*Hoxc\*-8 protein \*interaction\*, bone morphogenetic protein signal, antisense, antibody, appl. osteoporosis therapy, drug screening, gene expression regulation, gene transcription induction (Vol.20, No.15)

6/3,K/6 (Item 1 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

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134158510 CA: 134(12)158510m PATENT

12593175 BIOSIS NO.: 200000346677

**\*Smad6\* as a transcriptional corepressor.**

AUTHOR: Bai Shuting; Shi Xingming; Yang Xiangli; Cao Xu(a)

AUTHOR ADDRESS: (a)1670 University Blvd., VH G002, Birmingham, AL,  
35294-0019\*\*USA

JOURNAL: Journal of Biological Chemistry 275 (12):p8267-8270 March 24,  
2000

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

QP 501.57

**\*Smad6\* as a transcriptional corepressor.**

ABSTRACT: \*Smad6\* and Smad7, a subgroup of Smad proteins, antagonize the signals elicited by transforming growth factor-beta. These two Smads, induced by transforming growth factor-beta...

...protein (BMP) stimulation, form stable associations with their activated type I receptors, blocking phosphorylation of receptor-regulated Smads in the cytoplasm. Here we show that \*Smad6\* \*interacts\* with homeobox (Hox) c-8 as a transcriptional corepressor, inhibiting BMP signaling in the nucleus. The \*interaction\* between \*Smad6\* and \*Hoxc\*-8 was identified by a yeast two-hybrid approach and further demonstrated by co-immunoprecipitation assays in cells. Gel shift assays show that \*Smad6\*, but not Smad7, \*interacts\* with both \*Hoxc\*-8 and Hoxa-9 as a heterodimer when binding to DNA. More importantly, the \*Smad6\*-\*Hoxc\*-8 complex inhibits \*interaction\* of Smad1 with \*Hoxc\*-8- and Smad1-induced transcription activity. These data indicate that \*Smad6\* \*interacts\* with Hox transcription factors as part of the negative feedback circuit in the BMP signaling pathway.

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*Smad6\*--...

...\*Smad6\*-\*Hoxc\*-8 complex

6/3,K/3 (Item 3 from file: 5)

DIALOG(R)File 5:BIOSIS Previews(R)

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12136206 BIOSIS NO.: 199900431055

**\*Smad6\* \*interacts\* with \*Hoxc\*-8 as a transcriptional co-repressor in BMP signaling.**

AUTHOR: Bai Shuting(a); Shi Xingming(a); Yang Xiangli(a); Cao Xu(a)

AUTHOR ADDRESS: (a)Pathology, University of Alabama at Birmingham,  
Birmingham, AL\*\*USA

JOURNAL: Journal of Bone and Mineral Research 14 (SUPPL. 1):pS146 Sept.,  
1999

CONFERENCE/MEETING: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research St. Louis, Missouri, USA September 30-October 4, 1999

SPONSOR: American Society for Bone and Mineral Research

ISSN: 0884-0431

RECORD TYPE: Citation

LANGUAGE: English

**\*Smad6\* \*interacts\* with \*Hoxc\*-8 as a transcriptional co-repressor in BMP signaling.**

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*Hoxc\*-8...

...\*Smad6\*

6/3,K/4 (Item 1 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

**The interaction of Smad6 with Hox proteins and BMP signalling and uses thereof in regulation of bone formation**

INVENTOR(AUTHOR): Cao, Xu; Shi, Xingming; Bai, Shuting

LOCATION: USA

ASSIGNEE: Uab Research Foundation

PATENT: PCT International ; WO 0111013 A2 DATE: 20010215

APPLICATION: WO 2000US40563 (20000803) \*US PV147161 (19990804)

PAGES: 34 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-000/A

DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM ; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

?

\*Smad2\* and \*Smad3\* are phosphorylated by TGF-beta and activin receptors, whereas phosphorylation of \*Smad\* 1 is specifically induced by bone morphogenetic proteins. Upon phosphorylation these \*Smad\* proteins interact with a common partner, \*Smad4\*, and translocate into the nucleus where the complex recruits DNA binding protein(s) to activate specific gene transcription. However, the DNA binding protein(s) involved in BMP signaling has not been identified. We have demonstrated that BMPs induce the interaction of \*Smad1\* with Hoxc-8, a member of the homeodomain transcription factor family. The interaction of \*Smad\* 1 with Hoxc-8 inhibits the binding of Hoxc-8 to its DNA binding site. Hoxc-8 functions as a transcription repressor. A hox binding...

... osteopontin gene transcription is mediated through this Hox binding site. We hypothesize that BMP-2/4 induces osteoblast cell differentiation mediated by the \*Smad1\* interaction with Hoxc-8. The specific aims proposed are to: 1) characterize the specificity of the interaction between \*Smad1\* and Hox proteins in BMP2/4 signaling; 2) map domains that are responsible for the interaction between \*Smad1\* and \*Hoxc8\*. The effect of mapped \*Smad1\* interaction domains on gene transcription will also be assessed in luciferase reporter transfection studies. 3) Characterize the effects of the interaction between \*Smad1\* and Hoxc-8 on osteoblast differentiation in human primary stro-1 cells. Further characterization of the interaction between \*Smad1\* and Hoxc-8 will help us to understand the mechanism of BMP signaling and may yield a potential drug target to stimulate bone formation...

? s hox? and smad?

25540 HOX?

11121 SMAD?

S3 114 HOX? AND SMAD?

?rd

...examined 50 records (50)

...examined 50 records (100)

...completed examining records

S4 50 RD (unique items)

?s s4 and (inhibit? or repress? or suppress?)

Processing

Processed 10 of 42 files ...

Processing

Processed 20 of 42 files ...

Processing

Processed 40 of 42 files ...

Completed processing all files

50 S4

6695693 INHIBIT?

266501 REPRESS?

1690376 SUPPRESS?

S5 31 S4 AND (INHIBIT? OR REPRESS? OR SUPPRESS?)

?show files;ds;t/3,k/all

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     (c) 2002 Mass. Med. Soc.  
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     (c) 2001 Informania Ltd.

Set	Items	Description
S1	7	HOXC8 AND SMAD?
S2	7	RD (unique items)

S3 114 HOX? AND SMAD?  
S4 50 RD (unique items)  
S5 31 S4 AND (INHIBIT? OR REPRESS? OR SUPPRESS?)  
>>>KWIC option is not available in file(s): 41, 77, 399

5/3,K/1 (Item 1 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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13556490 BIOSIS NO.: 200200185311

**A nuclear antagonistic mechanism of \*inhibitory\* \*Smads\* in transforming growth factor-beta signaling.**

AUTHOR: Bai Shuting; Cao Xu(a)  
AUTHOR ADDRESS: (a)Dept. of Pathology, University of Alabama at Birmingham  
School of Medicine, 1670 University Blvd., VH G002, Birmingham, AL,  
35294-0019\*\*USA E-Mail: cao@path.uab.edu  
JOURNAL: Journal of Biological Chemistry 277 (6):p4176-4182 February 8,  
2002  
MEDIUM: print  
ISSN: 0021-9258  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

**A nuclear antagonistic mechanism of \*inhibitory\* \*Smads\* in transforming growth factor-beta signaling.**

ABSTRACT: \*Inhibitory\* \*Smads\* (I-\*Smads\*), including \*Smad6\* and \*Smad7\*, were initially characterized as cytoplasmic antagonists in the transforming growth factor-beta signaling pathway. However, I-\*Smads\* are also localized in the nucleus. Previously, we have shown that \*Smad6\* can function as a transcriptional co-\*repressor\*. In this study, we found both \*Smad6\* and \*Smad7\* interact with histone deacetylases (HDACs). Acetylation state of core histones plays a critical role in gene transcription regulation. An HDAC \*inhibitor\*, trichostatin A, released \*Smad6\*-mediated transcription \*repression\*. Moreover, class I HDACs (HDAC-1 and -3), not class II HDACs (HDAC-4, -5, and -6), were co-immunoprecipitated with \*Smad6\*. Endogenous HDAC-1 was also shown to interact with both \*Smad6\* and \*Hoxc\*-8. Mapping of the interaction domain indicates \*Smad6\* MH2 domain is mainly involved in recruiting HDAC-1. Most interestingly, \*Smad6\* also binds to DNA through its MH1 domain, and the MH2 domain of \*Smad6\* masks this binding activity, indicating that \*Smad6\* MH1 and MH2 domains associate reciprocally and \*inhibit\* each other's function. \*Hoxc\*-8 induces \*Smad6\* binding to DNA as a transcriptional complex. Our findings revealed that I-\*Smads\* act as antagonists in the nucleus by recruiting HDACs.

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*inhibitory\* \*Smads\*--  
MISCELLANEOUS TERMS: ...regulation mechanisms, \*repression\* mechanisms  
...

5/3,K/2 (Item 2 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
(c) 2002 BIOSIS. All rts. reserv.

13307638 BIOSIS NO.: 200100514787

**\*Inhibition\* of binding of \*Hox\* and homeodomain-containing proteins and uses thereof.**

AUTHOR: Cao Xu(a); Shi Xingming; Yang Xiangli  
AUTHOR ADDRESS: (a)Birmingham, AL\*\*USA  
JOURNAL: Official Gazette of the United States Patent and Trademark Office  
Patents 1250 (1):pNo Pagination Sep. 4, 2001  
MEDIUM: e-file  
ISSN: 0098-1133  
DOCUMENT TYPE: Patent  
RECORD TYPE: Abstract

LANGUAGE: English

**\*Inhibition\* of binding of \*Hox\* and homeodomain-containing proteins and uses thereof.**

ABSTRACT: The present invention demonstrates that BMP-2/4 activates osteopontin gene transcription by removing \*Hoxc\*-8 binding through \*Smad1\* interaction with the \*Hoxc\*-8 DNA binding domain. Since the DNA binding domain is conserved in all \*Hox\* and homeodomain-containing proteins, \*Smad1\* likely interacts with all \*Hox\* or homeodomain-containing proteins. Furthermore, the present invention reveals the \*Smad1\*-mediated transcriptional mechanism in the BMP-2/4 signaling pathway and also provides information about the transcriptional roles of the \*Hox\* genes during embryonic development.

...REGISTRY NUMBERS: \*SMAD\*-1

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*Hox\*-containing proteins...

...\*Hoxc\*-8 DNA binding domain...

...\*Smad\*-1

METHODS & EQUIPMENT: \*Smad1\*-mediated transcriptional mechanism...

**5/3,K/3 (Item 3 from file: 5)**

DIALOG(R) File 5:Biosis Previews(R)

(c) 2002 BIOSIS. All rts. reserv.

13076450 BIOSIS NO.: 200100283599

**\*Hoxa\*-9 \*represses\* transforming growth factor-beta-induced osteopontin gene transcription.**

AUTHOR: Shi Xingming; Bai Shuting; Li Lina; Cao Xu(a)

AUTHOR ADDRESS: (a)University of Alabama at Birmingham, 1670 University Blvd., Volker Hall/G002, Birmingham, AL, 35294: cao@path.uab.edu\*\*USA

JOURNAL: Journal of Biological Chemistry 276 (1):p850-855 January 5, 2001

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

**\*Hoxa\*-9 \*represses\* transforming growth factor-beta-induced osteopontin gene transcription.**

ABSTRACT: \*Smad2\* and \*Smad3\* are downstream transforming growth factor-beta (TGF-beta) signaling molecules. Upon phosphorylation by its type I receptor, \*Smad2\* or \*Smad3\* forms a complex with \*Smad4\* and translocates to the nucleus where the complex activates target gene transcription. In the present study, we report that \*Smad3\* binds directly to the osteopontin (OPN) promoter and that \*Smad4\* interacts with the \*Hox\* protein and displaces it from its cognate DNA binding site in response to TGF-beta stimulation. In gel shift assays, the glutathione S-transferase-\*Smad3\* fusion protein was found to bind to a 50-base pair DNA element (-179 to -229) from the OPN promoter. Also, we found that both \*Hoxc\*-8 and \*Hoxa\*-9 bound to a \*Hox\* binding site adjacent to \*Smad3\* binding sequence. Interestingly, \*Smad4\*, the common partner for both bone morphogenic protein and TGF-beta signaling pathways, \*inhibited\* the binding of \*Hox\* protein to DNA. FLAG-tagged \*Smad4\* coimmunoprecipitated with HA-tagged \*Hoxa\*-9 from cotransfected COS-1 cells, demonstrating an interaction between \*Smad4\* and \*Hoxa\*-9. Transfection studies showed that \*Hoxa\*-9 is a strong transcriptional \*repressor\*; it \*suppresses\* the transcription of the luciferase reporter gene driven by a 124-base pair OPN promoter fragment containing both \*Smad3\* and \*Hox\* binding sites. Taken together, these data demonstrate a unique TGF-beta-induced transcription mechanism. \*Smad3\* and \*Smad4\* exhibit different functions in activation of OPN transcription. \*Smad3\*

binds directly to the OPN promoter as a sequence-specific activator, and \*Smad4\* displaces the transcription \*repressor\*, \*Hoxa\*-9, by formation of \*Smad4\*/\*Hox\* complex as part of the transcription mechanism in response to TGF-beta stimulation.

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: \*Smad2\*--...

...\*Smad3\*--...

...\*Smad4\*; \*hoxa\*-9

**5/3,K/4 (Item 4 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

(c) 2002 BIOSIS. All rts. reserv.

13002597 BIOSIS NO.: 200100209746

**Transcriptional mechanisms of bone morphogenetic protein-induced osteoprotegrin gene expression.**

AUTHOR: Wan Mei; Shi Xingming; Feng Xu; Cao Xu(a)

AUTHOR ADDRESS: (a)1670 University Blvd., VH G002, Birmingham, AL, 35294-0019; Cao@path.uab.edu\*\*USA

JOURNAL: Journal of Biological Chemistry 276 (13):p10119-10125 March 30, 2001

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Osteoprotegerin (OPG), an osteoblast-secreted decoy receptor, specifically binds to osteoclast differentiation factor and \*inhibits\* osteoclast maturation. Members of the transforming growth factor-beta superfamily including bone morphogenetic proteins (BMPs) stimulate OPG mRNA expression. In this study, we have characterized the transcription mechanism of BMP-induced OPG gene expression. Transfection of \*Smad1\* and a constitutively active BMP type IA receptor ALK3 (Q233) stimulated the OPG promoter. Deletion analysis of the OPG promoter identified two \*Hoxc\*-8 binding sites that respond to BMP stimulation. Glutathione S-transferase-\*Hoxc\*-8 protein binds to these two \*Hox\* sites specifically. Consistent with the transfection results of the native promoter, ALK3 or \*Smad1\* linker region, which interacts with \*Hoxc\*-8, stimulated the activation of the reporter construct with the two \*Hox\* sites. Overexpression of \*Hoxc\*-8 \*inhibited\* the induced promoter activity. When the two \*Hox\* binding sites were mutated, ALK3 or \*Smad1\* linker region no longer activated the transcription. Importantly, \*Smad1\* linker region induced both OPG promoter activity and endogenous OPG protein expression in 2T3 osteoblastic cells. The medium from cells transfected with \*Smad1\* linker region expression plasmid effectively \*inhibited\* osteoclastogenesis. Collectively, our data indicate that \*Hox\* sites mediate both OPG promoter construct activity and endogenous OPG gene expression in response to BMP stimulation.

**5/3,K/5 (Item 5 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

(c) 2002 BIOSIS. All rts. reserv.

12864099 BIOSIS NO.: 200100071248

**TGFbeta and BMP-2 activation of the OPN promoter: Roles of \*Smad\*- and \*Hox\*-binding elements.**

AUTHOR: Hullinger Thomas G; Pan Quintin; Viswanathan Hema L; Somerman Martha J(a)

AUTHOR ADDRESS: (a)Periodontics/Prevention/Geriatrics, School of Dentistry, University of Michigan, 1011 N. University Avenue, Ann Arbor, MI, 48109-1078; somerman@umich.edu\*\*USA

JOURNAL: Experimental Cell Research 262 (1):p69-74 January 1, 2001  
MEDIUM: print  
ISSN: 0014-4827  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English  
SUMMARY LANGUAGE: English

**TGFbeta and BMP-2 activation of the OPN promoter: Roles of \*Smad\*- and \*Hox\*-binding elements.**

ABSTRACT: Members of the transforming growth factor superfamily are known to transduce signals via the activation of \*Smad\* proteins. Ligand binding to transmembrane cell surface receptors triggers the phosphorylation of pathway-specific \*Smads\*. These \*Smads\* then complex with \*Smad\* 4 and are translocated to the nucleus where they effect gene transcription. \*Smads\* 1 and 4 were recently demonstrated to mediate BMP activation of the OPN promoter by \*inhibiting\* the interaction of \*Hoxc\*-8 protein with a \*Hox\*-binding element. While previous studies have indicated that specific DNA sequences are recognized by \*Smad\* complexes in several promoters, the role of \*Smad\*-binding elements (SBEs) in activation of the OPN promoter by members of the TGFbeta superfamily has not been previously evaluated. In this study we tested the hypothesis that a putative \*Smad\*-binding region containing the sequence AGACTGTCTGGAC is involved in the activation of the OPN promoter by members of the TGFbeta superfamily. Functional analyses demonstrated that the both the HBE- and \*Smad\*-binding region were involved in BMP-2-induced activation of the promoter, whereas, the HBE appeared to be the primary region involved in activation by TGFbeta. Deletion of the first 9 bases in the \*Smad\*-binding region substantially reduced BMP-2-mediated activation of the promoter. These results strongly suggest that both the \*Hox\*- and the \*Smad\*-binding regions play a role in BMP-2-induced activation of the OPN promoter.

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: \*Hox\*-binding elements...  
...\*Smad\*-binding elements

5/3,K/6 (Item 6 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)  
(c) 2002 BIOSIS. All rts. reserv.

12655338 BIOSIS NO.: 200000408840

**Histone deacetylase (HDAC) mediates \*Smad6\* \*repressive\* function in BMP signaling pathway.**

AUTHOR: Bai S(a); Cao X(a)

AUTHOR ADDRESS: (a)Pathology, University of Alabama at Birmingham,  
Birmingham, AL\*\*USA

JOURNAL: Journal of Bone and Mineral Research 15 (Suppl. 1):pS205  
September, 2000

MEDIUM: print

CONFERENCE/MEETING: Twenty-Second Annual Meeting of the American Society  
for Bone and Mineral Research Toronto, Ontario, Canada September 22-26,  
2000

SPONSOR: American Society for Bone and Mineral Research

ISSN: 0884-0431

RECORD TYPE: Citation

LANGUAGE: English

SUMMARY LANGUAGE: English

**Histone deacetylase (HDAC) mediates \*Smad6\* \*repressive\* function in BMP signaling pathway.**

...REGISTRY NUMBERS: \*SMAD1\*;

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*Hoxc\*-8...

...\*Smad1\*--...

...\*Smad6\*--...

...overexpression, \*repressive\* function

**5/3,K/7 (Item 7 from file: 5)**  
DIALOG(R)File 5:Biosis Previews(R)  
(c) 2002 BIOSIS. All rts. reserv.

12655336 BIOSIS NO.: 200000408838

**\*Hoxa\*-9 interacts with \*Smad4\* and \*inhibits\* TGF-beta-induced osteopontin gene transcription.**

AUTHOR: Shi X(a); Yang X(a); Bai S(a); Li L(a); Cao X(a)

AUTHOR ADDRESS: (a)University of Alabama, Birmingham, AL\*\*USA

JOURNAL: Journal of Bone and Mineral Research 15 (Suppl. 1):pS172

September, 2000

MEDIUM: print

CONFERENCE/MEETING: Twenty-Second Annual Meeting of the American Society for Bone and Mineral Research Toronto, Ontario, Canada September 22-26, 2000

SPONSOR: American Society for Bone and Mineral Research

ISSN: 0884-0431

RECORD TYPE: Citation

LANGUAGE: English

SUMMARY LANGUAGE: English

**\*Hoxa\*-9 interacts with \*Smad4\* and \*inhibits\* TGF-beta-induced osteopontin gene transcription.**

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: \*Hoxa\*-9...

...\*Smad3\*; \*Smad4\*;

**5/3,K/8 (Item 8 from file: 5)**  
DIALOG(R)File 5:Biosis Previews(R)  
(c) 2002 BIOSIS. All rts. reserv.

12593175 BIOSIS NO.: 200000346677

**\*Smad6\* as a transcriptional corepressor.**

AUTHOR: Bai Shuting; Shi Xingming; Yang Xiangli; Cao Xu(a)

AUTHOR ADDRESS: (a)1670 University Blvd., VH G002, Birmingham, AL,  
35294-0019\*\*USA

JOURNAL: Journal of Biological Chemistry 275 (12):p8267-8270 March 24, 2000

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

**\*Smad6\* as a transcriptional corepressor.**

ABSTRACT: \*Smad6\* and \*Smad7\*, a subgroup of \*Smad\* proteins, antagonize the signals elicited by transforming growth factor-beta. These two \*Smads\*, induced by transforming growth factor-beta or bone morphogenetic protein (BMP) stimulation, form stable associations with their activated type I receptors, blocking phosphorylation of receptor-regulated \*Smads\* in the cytoplasm. Here we show that \*Smad6\* interacts with homeobox (\*Hox\*) c-8 as a transcriptional corepressor, \*inhibiting\* BMP signaling in the nucleus. The interaction between \*Smad6\* and \*Hoxc\*-8 was identified by a yeast two-hybrid approach and further demonstrated by co-immunoprecipitation assays in cells. Gel shift assays show that \*Smad6\*, but not \*Smad7\*, interacts with both \*Hoxc\*-8 and \*Hoxa\*-9 as a heterodimer when binding to DNA. More importantly, the \*Smad6\*-\*\*Hoxc\*-8 complex \*inhibits\* interaction of \*Smad1\* with \*Hoxc\*-8- and \*Smad1\*

-induced transcription activity. These data indicate that \*Smad6\* interacts with \*Hox\* transcription factors as part of the negative feedback circuit in the BMP signaling pathway.

...REGISTRY NUMBERS: \*SMAD1\*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*Hox\* transcription factors...

...\*Smad1\*; \*Smad6\*--...

...\*Smad6\*--\*Hoxc\*-8 complex...

...\*Smad7\*--

**5/3,K/9 (Item 9 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

(c) 2002 BIOSIS. All rts. reserv.

12149499 BIOSIS NO.: 199900444348

**\*Smad4\* interacts with \*Hoxa\*-9 in TGF-beta signaling pathway.**

AUTHOR: Shi X(a); Yang X(a); Bai S(a); Li L(a); Cao X(a)

AUTHOR ADDRESS: (a)Department of Pathology, University of Alabama at Birmingham, Birmingham, AL\*\*USA

JOURNAL: Journal of Bone and Mineral Research 14 (SUPPL. 1):pS299 Sept., 1999

CONFERENCE/MEETING: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research St. Louis, Missouri, USA September 30-October 4, 1999

SPONSOR: American Society for Bone and Mineral Research

ISSN: 0884-0431

RECORD TYPE: Citation

LANGUAGE: English

**\*Smad4\* interacts with \*Hoxa\*-9 in TGF-beta signaling pathway.**

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*Hox\* proteins...

...\*Hoxa\*-9...

...transcription \*repressing\* effects...

...\*Smad3\*--...

...\*Smad4\*--\*Hox\* complex formation

**5/3,K/10 (Item 10 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

(c) 2002 BIOSIS. All rts. reserv.

12136206 BIOSIS NO.: 199900431055

**\*Smad6\* interacts with \*Hoxc\*-8 as a transcriptional co-\*repressor\* in BMP signaling.**

AUTHOR: Bai Shuting(a); Shi Xingming(a); Yang Xiangli(a); Cao Xu(a)

AUTHOR ADDRESS: (a)Pathology, University of Alabama at Birmingham, Birmingham, AL\*\*USA

JOURNAL: Journal of Bone and Mineral Research 14 (SUPPL. 1):pS146 Sept., 1999

CONFERENCE/MEETING: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research St. Louis, Missouri, USA September 30-October 4, 1999

SPONSOR: American Society for Bone and Mineral Research

ISSN: 0884-0431

RECORD TYPE: Citation

LANGUAGE: English

**\*Smad6\* interacts with \*Hoxc\*-8 as a transcriptional co-\*repressor\* in BMP signaling.**

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*Hoxc\*-8...  
...\*Smad6\*

**5/3,K/11 (Item 11 from file: 5)**  
DIALOG(R) File 5:Biosis Previews(R)  
(c) 2002 BIOSIS. All rts. reserv.

11982459 BIOSIS NO.: 199900262978

**\*Smad1\* interacts with homeobox DNA-binding proteins in bone morphogenetic protein signaling.**

AUTHOR: Shi Xingming; Yang Xiangli; Chen Di; Chang Zhijie; Cao Xu(a)

AUTHOR ADDRESS: (a)1670 University Blvd., VH G002, Birmingham, AL,  
35294-0019\*\*USA

JOURNAL: Journal of Biological Chemistry 274 (19):p13711-13717 May 7, 1999

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

**\*Smad1\* interacts with homeobox DNA-binding proteins in bone morphogenetic protein signaling.**

ABSTRACT: Bone morphogenetic proteins (BMP) transduce their signals into the cell through a family of mediator proteins known as \*Smads\*. Upon phosphorylation by the BMP receptors, \*Smad1\* interacts with \*Smad4\* and translocates into the nucleus where the complex recruits DNA-binding protein(s) to activate specific gene transcription. However, the DNA-binding protein(s) involved in BMP signaling has not been identified. Using a yeast two-hybrid approach, we found that \*Smad1\* interacts with \*Hoxc\*-8, a homeodomain transcription factor. The interaction between \*Smad1\* and \*Hoxc\*-8 was confirmed by a "pull-down" assay and a co-immunoprecipitation experiment in COS-1 cells. Interestingly, purified \*Smad1\* \*inhibited\* \*Hoxc\*-8 binding to the osteopontin \*Hoxc\*-8 site in a concentration-dependent manner. Transient transfection studies showed that native osteopontin promoter activity was elevated upon BMP stimulation. Consistent with the gel shift assay, overexpression of \*Hoxc\*-8 abolished the BMP stimulation. When a wild type or mutant \*Hoxc\*-8 binding element was linked to an SV40 promoter-driven reporter gene, the wild type but not the mutant \*Hoxc\*-8 binding site responded to BMP stimulation. Again, overexpression of \*Hoxc\*-8 \*suppressed\* the BMP-induced activity of the wild type reporter construct. Our findings suggest that \*Smad1\* interaction with \*Hoxc\*-8 dislodges \*Hoxc\*-8 from its DNA binding element, resulting in the induction of gene expression.

...REGISTRY NUMBERS: \*SMAD1\*;

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*Hoxc\*-8...

...\*Smad1\*

**5/3,K/12 (Item 1 from file: 34)**  
DIALOG(R) File 34:SciSearch(R) Cited Ref Sci  
(c) 2002 Inst for Sci Info. All rts. reserv.

10019375 Genuine Article#: 476HL No. References: 64

**Title: The \*Smad\* transcriptional corepressor TGIF recruits mSin3**

Author(s): Wotton D (REPRINT) ; Knoepfler PS; Laherty CD; Eisenman RN;  
Massague J

Corporate Source: Univ Virginia, Dept Biochem & Mol Genet, 800577

HSC/Charlottesville//VA/22908 (REPRINT); Univ Virginia, Dept Biochem &

Mol Genet, Charlottesville//VA/22908; Univ Virginia, Ctr Cell

Signaling, Charlottesville//VA/22908; Fred Hutchinson Canc Res Ctr, Div

Basic Sci, Seattle//WA/98109; Mem Sloan Kettering Canc Ctr, Howard Hughes

Med Inst, Cell Biol Program, New York//NY/10021



Journal: CELL GROWTH & DIFFERENTIATION, 2001, V12, N9 (SEP), P457-463  
ISSN: 1044-9523 Publication date: 20010900  
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202  
USA  
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

**Title: The \*Smad\* transcriptional corepressor TGIF recruits mSin3**

Abstract: The homeodomain protein TG-interacting factor (TGIF) \*represses\* transcription by histone deacetylase-dependent and -independent means. Heterozygous mutations in human TGIF result in holoprosencephaly, a severe genetic disorder affecting craniofacial development, suggesting that TGIF is critical for normal development. After transforming growth factor beta (TGF beta) stimulation, \*Smad\* proteins enter the nucleus and form transcriptional activation complexes or interact with TGIF, which functions as a corepressor. The relative levels of \*Smad\* corepressors and coactivators present within the cell may determine the outcome of a TGF beta response. We show that TGIF interacts directly with the paired amphipathic alpha-helix 2 domain of the mSin3 corepressor, and TGIF recruits mSin3 to a TGF beta-activated \*Smad\* complex. The mSin3 interaction domain of TGIF has been shown to be essential for \*repression\* of a TGF beta transcriptional response. Thus, TGIF represents a targeting component of the mSin3 corepressor complex.

...Identifiers--HISTONE DEACETYLASE; DNA-BINDING; N-COR; \*REPRESS\* TRANSCRIPTION; MEDIATES \*REPRESSION\*; COMPLEX-FORMATION; PBX PROTEINS; SIN3; \*HOX; \*MAD

**5/3,K/13 (Item 2 from file: 34)**

DIALOG(R) File 34:SciSearch(R) Cited Ref Sci  
(c) 2002 Inst for Sci Info. All rts. reserv.

09926645 Genuine Article#: 465WT No. References: 49

**Title: TGIF2 interacts with histone deacetylase I and \*represses\* transcription**

Author(s): Melhuish TA; Gallo CM; Wotton D (REPRINT)  
Corporate Source: Univ Virginia, Hosp W, Ctr Cell Signaling, Box 800577  
HSC/Charlottesville//VA/22908 (REPRINT); Univ Virginia, Dept Biochem &  
Mol Genet, Charlottesville//VA/22908; Univ Virginia, Ctr Cell  
Signaling, Charlottesville//VA/22908

Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 2001, V276, N34 (AUG 24), P  
32109-32114

ISSN: 0021-9258 Publication date: 20010824

Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE  
PIKE, BETHESDA, MD 20814 USA

Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

**Title: TGIF2 interacts with histone deacetylase I and \*represses\* transcription**

Abstract: TG-interacting factor (TGIF) is a transcriptional \*repressor\*, which \*represses\* transcription by binding directly to DNA or interacts with transforming growth factor beta (TGF beta)-activated \*Smads\*, thereby \*repressing\* TGF beta-responsive gene expression. Mutation of TGIF in humans causes holoprosencephaly, a severe genetic disorder affecting craniofacial development. Searching human expressed sequence tag data...

...deacetylase, but in contrast to TGIF, is unable to interact with the corepressor CtBP. TGIF2 and TGIF have very similar DNA-binding homeodomains, and TGIF2 \*represses\* transcription when bound to DNA via a TGIF binding site. TGIF2 interacts with TGF beta-activated \*Smads\* and \*represses\* TGF beta-responsive transcription. TGIF2 appears to be a context-independent transcriptional \*repressor\*, which can perform similar functions to TGIF and may play a role in processes, which, when disrupted by mutations in TGIF, cause holoprosencephaly.

...Identifiers--GROWTH-FACTOR-BETA; HOMEODOMAIN PROTEINS;  
\*SMAD\* PROTEINS; TUMOR-\*SUPPRESSOR\*; TALE SUPERCLASS; COREPRESSOR;

5/3,K/14 (Item 3 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci  
(c) 2002 Inst for Sci Info. All rts. reserv.

09259028 Genuine Article#: 384PB No. References: 56

**Title: The interaction of the carboxyl terminus-binding protein with the \*Smad\* corepressor TGIF is disrupted by a holoprosencephaly mutation in TGIF**

Author(s): Melhuish TA; Wotton D (REPRINT)

Corporate Source: Univ Virginia, Hosp West, Ctr Cell Signaling, HSC, Box 800577/Charlottesville//VA/22908 (REPRINT); Univ Virginia, Dept Biochem & Mol Genet, Charlottesville//VA/22908; Univ Virginia, Ctr Cell Signaling, Charlottesville//VA/22908

Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 2000, V275, N50 (DEC 15), P 39762-39766

ISSN: 0021-9258 Publication date: 20001215

Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA

Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

**Title: The interaction of the carboxyl terminus-binding protein with the \*Smad\* corepressor TGIF is disrupted by a holoprosencephaly mutation in TGIF**

**Abstract:** The homeodomain protein TGIF \*represses\* transcription in part by recruiting histone deacetylases. TGIF binds directly to DNA to \*repress\* transcription or interacts with TGF-beta -activated \*Smads\*, thereby \*repressing\* genes normally activated by TGF-beta. Loss of function mutations in TGIF result in holoprosencephaly (HPE) in humans. One HPE mutation in TGIF results in a single amino acid substitution in a conserved PLDLS motif within the amino-terminal \*repression\* domain. We demonstrate that TGIF interacts with the corepressor carboxyl terminus-binding protein (CtBP) via this motif. CtBP, which was first identified by its ability to bind the adenovirus E1A protein, interacts both with gene-specific transcriptional \*repressors\* and with a subset of polycomb proteins. Efficient \*repression\* of TGF-beta -activated gene responses by TGIF is dependent on interaction with CtBP, and we show that TGIF is able to recruit CtBP to a TGF-beta -activated \*Smad\* complex. Disruption of the PLDLS motif in TGIF abolishes the interaction of CtBP with TGIF and compromises the ability of TGIF to \*repress\* transcription. Thus, at least one HPE mutation in TGIF appears to prevent CtBP-dependent transcriptional \*repression\* by TGIF, suggesting an important developmental role for the recruitment of CtBP by TGIF.

...Identifiers--DNA-BINDING; TRANSCRIPTIONAL \*REPRESSOR\*; CELLULAR PHOSPHOPROTEIN; NEGATIVE MODULATION; BETA; \*HOX; \*HOMEODOMAIN; COMPLEXES; DOMAIN; PBX

5/3,K/15 (Item 4 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci  
(c) 2002 Inst for Sci Info. All rts. reserv.

08295062 Genuine Article#: 267WR No. References: 42

**Title: Multiple modes of \*repression\* by the \*Smad\* transcriptional corepressor TGIF**

Author(s): Wotton D; Lo RS; Swaby LAC; Massague J (REPRINT)

Corporate Source: MEM SLOAN KETTERING CANC CTR, HOWARD HUGHES MED INST, CELL BIOL PROGRAM, BOX 116, 1275 YORK AVE/NEW YORK//NY/10021 (REPRINT); MEM SLOAN KETTERING CANC CTR, HOWARD HUGHES MED INST, CELL BIOL PROGRAM/NEW YORK//NY/10021

Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 1999, V274, N52 (DEC 24), P 37105-37110

ISSN: 0021-9258 Publication date: 19991224

Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE

**Title: Multiple modes of \*repression\* by the \*Smad\* transcriptional corepressor TGIF**

...Abstract: responsive transcription. We investigated the intrinsic transcriptional activity of TGIF fused to a heterologous DNA-binding domain. Our results demonstrate that TGIF is a transcriptional \*repressor\* able to \*repress\* transcription from several different promoters. \*Repression\* by TGIF is insensitive to the distance at which it is bound from the promoter. Moreover, the wild type TGIF effectively \*represses\* transcription when bound to its cognate DNA-binding site via its homeodomain. Deletion analysis revealed the presence of at least two separable \*repression\* domains within TGIF, \*Repression\* by one of these is dependent on the activity of histone deacetylases (HDACs), whereas the other appears not to require HDAC activity. Finally, we demonstrate that TGIF interacts with HDACs via its carboxyl-terminal \*repression\* domain. Together, these results suggest that TGIF is a multifunctional transcriptional \*repressor\*, which acts in part by recruiting HDAC activity.

...Identifiers--TATA-BINDING PROTEIN; HISTONE DEACETYLASE; HOMEODOMAIN PROTEINS; N-COR; COMPLEX; SEQUENCE; DOMAIN; \*HOX; \*COACTIVATORS

**5/3,K/16 (Item 5 from file: 34)**

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci  
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08164078 Genuine Article#: 232CA No. References: 0

**Title: \*Smad6\* interacts with \*Hoxc\*-8 as a transcriptional go-\*repressor\* in BMP signaling.**

Author(s): Bai ST; Shi XM; Yang XL; Cao X  
Corporate Source: UNIV ALABAMA,/BIRMINGHAM//AL/  
Journal: JOURNAL OF BONE AND MINERAL RESEARCH, 1999, V14, 1 (SEP), P 1053-1053  
ISSN: 0884-0431 Publication date: 19990900  
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148  
Language: English Document Type: MEETING ABSTRACT

**Title: \*Smad6\* interacts with \*Hoxc\*-8 as a transcriptional go-\*repressor\* in BMP signaling.**

**5/3,K/17 (Item 6 from file: 34)**

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci  
(c) 2002 Inst for Sci Info. All rts. reserv.

07287728 Genuine Article#: 146HR No. References: 32

**Title: Profiling of differentially expressed genes in human primary cervical cancer by complementary DNA expression array**

Author(s): Shim C; Zhang W; Rhee CH; Lee JH (REPRINT)  
Corporate Source: SUNG KYUN KWAN UNIV,SAMSUNG MED CTR, COLL MED, DEPT OBSTET & GYNECOL, KANGNAM KU, 50 ILWON DONG/SEOUL 135710//SOUTH KOREA/ (REPRINT); SUNG KYUN KWAN UNIV,SAMSUNG MED CTR, COLL MED, DEPT OBSTET & GYNECOL, KANGNAM KU/SEOUL 135710//SOUTH KOREA/; SUNG KYUN KWAN UNIV,SAMSUNG MED CTR, SAMSUNG BIOMED RES INST, CLIN RES CTR/SEOUL 135710//SOUTH KOREA/; UNIV TEXAS,MD ANDERSON CANC CTR, DEPT NEUROONCOL/HOUSTON//TX/77030  
Journal: CLINICAL CANCER RESEARCH, 1998, V4, N12 (DEC), P3045-3050  
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Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202  
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

...Abstract: the human cenix. These include myc protooncogene, 40S ribosomal protein S19, heat shock proteins, leukosialin S (CD43), integrin alpha L (CD11A), calgranulin (A), and CDK4 \*inhibitor\*

(p16(ink4)). No detectable changes were observed in the expression levels of these genes. Several mRNAs, such as those encoding guanine nucleotide-binding protein Gs (alpha, subunit), leukocyte adhesion protein (LFA1-beta), nuclear factor NF45, homeobox protein \*Hox\*-A1, and beta-catenin were detected in increased levels in cervical cancer. Genes that showed decreased expression in cervical cancer tissue were a group of apoptosis-related proteins, cell adhesion molecules, nuclear transcription factors, and a homeobox protein (\*Hox7\*). For example, the expression levels of \*Smad1\* and \*Hox7\* were consistently decreased in all tumor tissues tested. Northern analysis of \*Smad1\* and \*Hox7\* RNA in primary cervical tumor tissues and cervical carcinoma cell lines indicated that, in general, the mRNA levels of these genes were decreased in human...

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DIALOG(R)File 77:Conference Papers Index  
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4564292

Supplier Accession Number: 01-01944 V29N02

**Hoxa-9 interacts with Smad4 and inhibits TGF-b-induced osteopontin gene transcription**

Shi, X.

22nd Annual Meeting of the American Society for Bone and Mineral Research  
0005303 Toronto (Canada) 23-26 Sep 2000

American Society for Bone and Mineral Research

American Society for Bone and Mineral Research, 2025 M Street, NW, Suite 800, Washington, DC 20036-3309, USA; phone: (202) 367-1161; fax: (202) 367-2161 ; email: asbmr@dc.sba.com; URL: <http://www.asbmr.org>

**5/3,K/19 (Item 1 from file: 98)**  
DIALOG(R)File 98:General Sci Abs/Full-Text  
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04751953 H.W. WILSON RECORD NUMBER: BGSA02001953 (USE FORMAT 7 FOR FULLTEXT)

**Conservation and divergence in molecular mechanisms of axis formation**

Lall, Sabbi

Patel, Nipam H

Annual Review of Genetics v. 35 (2001) p. 407-37

SPECIAL FEATURES: bibl il ISSN: 0066-4197

LANGUAGE: English

COUNTRY OF PUBLICATION: United States

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TEXT:

... pelle, the end result of which is the phosphorylation and degradation of the Ikb orthologue cactus (10, 53, 126).

Cactus physically interacts with and thereby \*inhibits\* a key gene in dorsoventral axis formation, the morphogenetic transcription factor Dorsal (a NF k B/rel homologue: 170). Degradation of Cactus allows Dorsal to...

...embryo (Figure 2b). At highest nuclear concentration (ventral), Dorsal activates twist and snail, which are required for specification of ventral fate (mesoderm) and for the \*inhibition\* of lateral fates such as neurectoderm (48, 66, 80, 87, 104, 124, 125, 180-182). Laterally, intermediate nuclear concentrations of Dorsal activate a second group...

...sog). These genes specify lateral neurectodermal territories and influence the activity of Decapentaplegic (Dpp), respectively (see below; 42, 65). Dorsal also acts as a transcriptional \*repressor\* of genes such as dpp and zen, which specify dorsal fates (32, 64, 68, 125, 136). Thus, higher Dorsal nuclear activity in ventral and lateral...mediate the

transcriptional response to Dpp signaling (107, 108, 123, 154). Between them, the Mad/Medea and schnurri DNA binding transcription factors mediate activation and \*repression\* of dpp-responsive transcriptional targets (27, 61, 77, 93, 107, 108, 123, 154, 184). Mad family genes seem to collaborate with a variety of transcriptional cofactors and are more generally required for Dpp signaling than schnurri, which functions in part by antagonizing the general \*repression\* of dpp transcriptional targets by brinker (71, 93). Some of the above components have been isolated not only from other insect species, but also from...

...abdominal field of the embryo (72, 139). Thus there is potentially a more compelling argument for DV patterning by dpp during later development.

Evidence for \*repression\* of Tc-dpp by Dorsal protein can be inferred from the fact that Tc-dpp is not co-expressed in most cells with nuclear Tc-Dorsal (23). Although one could argue against \*repression\* of Tc-dpp by Tc-Dorsal as they are co-expressed in terminal cells, both dpp and nuclear Dorsal are also found in terminal cells...BMP/Chordin mirrors the Drosophila Dpp/Sog interaction in patterning the DV axis. Thus the chordin (chordin) mutant leads to ventralization, a phenotype that is \*suppressed\* by the swirl (BMP2) mutant (51, 78, 149).

Further levels of conservation are revealed upon examining Chordin regulation. A Xenopus tolloid homologue is capable of cleaving Chordin, thereby overriding Chordin \*inhibition\* of BMP4 (117). More recently, conservation of the twisted gastrulation gene has also been demonstrated. In contrast to initial data, twisted gastrulation may be a conserved \*inhibitor\* of BMP function. Some evidence indicates that it is responsible for producing a differential cleavage product of Sog/Chordin that may have increased anti-Dpp...

...twist orthologues have been isolated from chordates including mouse and Xenopus, they are expressed in and seem to activate specific mesodermal derivatives, and may also \*inhibit\* some myogenesis (for example, see 59, 191), twist may therefore control submesodermal fates rather than acting as a mesoderm or ventral specification factor in the...zygotic hunchback (hb), which bcd transcriptionally activates in an anterior domain (33). Like Bcd, hb provides information for anterior patterning through gap, pair-rule, and \*hox\* genes (reviewed in 127, 157, 173). Bcd is also responsible for the anterior translational \*repression\* of ubiquitous maternal caudal mRNA leading to a posterior gradient of the homeoprotein transcription factor Caudal (34, 129). caudal is involved in posterior patterning through...suggest that the bcd gene arose relatively recently. Phylogenetic analysis of the Megaloptera abdita bicoid and zen orthologues suggests that they are products of a \*Hox3\* duplication in an ancestor of the higher dipterans (167). bcd and zen reside together in the part of D. melanogaster \*Hox\* cluster in the location where one should find a \*Hox3\* orthologue. This adds support to the idea that the two genes are products of a \*Hox3\* duplication. Furthermore, the region of the Tribolium \*hox\* cluster in which one would expect to find bcd has now been sequenced and no bcd orthologue was found (16). Although the Tribolium orthologue could...

...interesting but unresolved). The mechanism by which bcd might have become involved in AP axis formation is discussed below and by Schmidt-Ott (145). The \*Hox3\* orthologue has been cloned from two chelicerates, a mite and a spider (28, 179). \*Hox3\* in chelicerates is expressed in a discrete domain of the AP axis, but its anterior border coincides with the \*Hox\* gene proboscopedial (pb). Thus, although \*Hox3\* in chelicerates is found in a \*hox\*-like expression domain, it is expressed more anteriorly than expected, suggesting a breakdown in colinear expression of this gene within the arthropods. Overlap with pb and the breakdown of colinearity are hypothesized to have allowed \*Hox3\* to lose \*hox\* function and take on novel roles in the lineage leading to insects (28, 179).

What does this tell us about the way in which the...

...highly conserved. The ancestral patterning system in insects may have involved a posterior caudal gradient and an anterior hb gradient. The duplication of an ancestral \*Hox3\* gene may have given rise to bcd, which in the modern fly plays a dual role as translational regulator of maternal

caudal, and transcriptional activator...

...As mentioned above, the Bcd gradient is crucial to generating the zygotic hb pattern. The earliest differential hb expression is, however, due to the translational \*repression\* of a uniform maternal pool of hb transcript (Figure 4) (see 176, 178). This translational \*repression\* is mediated by nanos, and its cofactor pumilio (62, 67, 102). Pumilio recognizes a sequence (NRE) in the 3'UTR of hb transcript, and forms is maternally localized to the posterior of the developing oocyte and translationally \*repressed\* anteriorly, a Nanos protein gradient forms emanating from the posterior (Figure 4) (26, 185). Hence, maternal hb transcript is translationally \*repressed\* at the posterior, leading to an anterior gradient of Hb protein.

Thus two systems, an anterior and a posterior system, independently generate an anterior Hb...

...hb in this domain. However, if extra copies of hb are supplied, and the levels of hb further increased by reducing levels of a transcriptional \*repressor\* of zygotic hb (knirps), the need for bcd in thoracic development is abrogated (190). Thus hb can almost entirely compensate for the anterior system during...

...N.H.P., unpublished observation). Thus while the bcd system seems a recent innovation in axis formation, setting up a gradient of Hb using translational \*repression\* by Nanos seems to be a more ancestral mechanism. What we may be observing in *D. melanogaster* is an intermediate in the displacement of an...

...145, 167). These data place the origin of amnioserosa and its DV axis location in the same phylogenetic position as the hypothesized duplication of a \*Hox3\* group gene to give bcd and zen (167). This gene duplication may also have been essential for relocation of extraembryonic material from the anterior region...to control the nuclear localization of Dorsal protein along the DV axis. (b) Dorsal is found in a nuclear gradient. At high nuclear concentrations Dorsal \*represses\* zygotic genes that pattern the dorsal regions of the embryo while activating ventral development through twist and snail activation. At intermediate levels the Dorsal transcription ...

...anterior system (key gene bicoid) leads to the localized activation of zygotic hb transcription and maternal caudal translational control. The posterior system involves the translational \*repression\* of maternal hunchback transcript. The resulting Hunchback protein gradient has an effect on zygotic caudal transcription. Anterior is to the left, posterior to the right...

...anterior system. The scheme envisages an ancestral state (bubble boxes, top row) where hunchback was involved in neural patterning, caudal in posterior patterning, and a \*Hox3\* gene in segmental identity along the AP axis. In the lineage leading to insects, hunchback and caudal may both have been involved in axial patterning, whereas \*Hox3\* became expressed in a spatial pattern that is no longer colinear with other \*Hox\* genes (middle row). In the lineage leading to the higher dipterans, the duplication of \*Hox3\* may have led to bicoid, which acts in the modern fly as a major player in AP axis formation through the regulation of hunchback and...

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**5/3,K/20 (Item 2 from file: 98)**

DIALOG(R)File 98:General Sci Abs/Full-Text

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04508074 H.W. WILSON RECORD NUMBER: BGSA01008074 (USE FORMAT 7 FOR FULLTEXT)

**Molecular regulation of lung development.**

Cardoso, Wellington V

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COUNTRY OF PUBLICATION: United States

WORD COUNT: 11669

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TEXT:

... pancreatic development, the day 7.5 endoderm receives patterning signals from the neighboring notochord. The notochord secretes activin-bB and FGF-2, which in turn \*inhibit\* Sonic hedgehog (Shh) signaling in the pre-pancreatic dorsal endoderm, and initiate a program of pancreatic gene expression (35). Surgical deletion of the notochord in...FGF-7 as a mitogen in lung epithelial cells (85, 117). Interestingly, at least in keratinocytes, heparin enhances the mitogenic activity of FGF-10 while \*inhibiting\* that of FGF-7 (40).

Whether proliferation is the primary driving force for lung epithelial budding has been debated. Experiments using mesenchyme-free lung epithelial ...expressed in both mesenchyme and the epithelium. Dynamic expression of FGF-10 might result from a combination of local induction and restriction of expression by \*inhibitors\*.

Although \*inhibitors\* of FGF-10 gene expression have been identified (see below), to date FGF-10 inducers have not yet been reported in the lung. Interestingly, if...

...levels of FGF-7 mRNA, assessed within the same period (53, 92). The data suggest that the developing lung epithelium has diffusible factors that are \*inhibitory\* for FGF-10 and stimulatory for FGF-7. There is evidence that mesenchymal factors also influence FGF-10 expression and its effects in the epithelium...birth, high levels of FGF-7 and low levels of Shh and Ptc are detected (5, 6, 11, 85). Whether FGF-7 functions as an \*inhibitory\* factor of Shh signaling in vivo remains to be determined.

Bone Morphogenetic Protein-4 (BMP-4) BMPs belong to the TGFb superfamily of growth factors...

...period of bud extension (117). Thus BMP-4 appears to be unnecessary for bud induction. Type I and type II serine-threonine kinase receptors and \*Smad\* transcription factors transduce BMP-4 signaling (reviewed in 58). Disruption of BMP-4 signaling in the lung of transgenic mice disrupts the proximaldistal pattern of growth and differentiation of the lung. Mice expressing either a dominant-negative type I BMP receptor (Alk6) or a secreted BMP-4 \*inhibitor\* Xenopus noggin (Xnoggin) under the control of the SP-C promoter do not properly form distal lung. In these mice, proximal cell types, such as...

...regulates BMP-4 expression in the distal epithelium and induces ectopic expression of BMP-4 in proximal epithelial explants (53, 117). Moreover, recombinant BMP-4 \*inhibits\* epithelial cell proliferation and prevents budding, thus antagonizing the effect of FGF-10 in epithelial explants (117). Presumably, FGF-10 -BMP-4 interaction serves to...

...at least two other members, all expressed in the developing lung. TGFb signaling is mediated by serine-threonine kinase receptors (type I and II) and \*Smad\* transcription factors (reviewed in 58). Activation of TGFb signaling is \*inhibitory\* for epithelial branching; expression of a dominant-negative TGFb RII in lung organ cultures stimulates branching morphogenesis (127). In the day 11-12 embryonic lung...

...TGFb-1 has also been identified as a potent negative regulator of epithelial cell proliferation and differentiation in vitro and in vivo. Recombinant TGFb-1 \*inhibits\* branching morphogenesis in cultured lung explants (97). When TGFb-1 is mis-expressed in the distal lung epithelium of transgenic mice, lungs do not develop...

...embryonic lung, TGFb-1 signals are present in the subepithelial mesenchyme, a site where FGF-10 is normally not expressed. Furthermore, recombinant TGFb-1 markedly \*inhibits\* FGF-10 expression, both in lung embryonic mesenchymal cell and in lung organ cultures (53). Therefore, TGFb-1 potentially exerts its effect on lung morphogenesis by at least three mechanisms: limiting epithelial bud proliferation, \*inhibiting\* FGF-10-mediated chemoattraction, and synthesizing extracellular matrix components that stabilize clefts (Figure 1).

Sprouty (Spry) Spry genes encode a family of cysteine-rich proteins

that antagonize FGF signaling. In Drosophila, Spry is induced by FGF signaling at the tips of branching tracheal tubules and \*inhibits\* lateral budding by a mechanism currently not well understood (34). At least three related murine genes, mSpry 1, 2, and 4, have been identified in...

...This appears to result from activation of mechanisms that antagonize RA signaling, such as increased RA degradation in the epithelium via P450RAI-mediated metabolism and \*inhibition\* of ...RA (10-6-10-5M) results in dramatic disruption of distal budding and formation of proximal-like immature airways (10, 56). In these cultures, RA \*inhibits\* expression and alters distribution of FGF-10 and BMP-4, pattern-related genes that are involved in distal lung morphogenesis. It is also noteworthy that...

...2 pattern is non-overlapping with that of FGF-10, supporting the idea that RA signaling restricts FGF-10 expression and may have to be \*inhibited\* to allow proper distal lung morphogenesis.

The mechanism involved in RA-induced \*inhibition\* of FGF-10 may be mediated by up-regulation of Shh, although there are data suggesting a Shh-independent pathway (6, 11, 56). The RA effect on pattern formation appears to involve signaling by RAR $\beta$ ; the \*inhibitory\* effect of exogenous RA on distal bud formation in vitro is reduced in lungs of RAR $\beta$  knockout mice. RA also alters expression of \*Hox\* genes in the lung (7, 11, 84), but how these changes influence the lung phenotype remains to be determined. \*Hox\* proteins regulate anterior-posterior specification of the body axis during development. Several \*Hox\* genes are expressed in the lung (reviewed in 9, 45); however, to date, only \*Hoxa\*-5 has shown a lung phenotype (laryngotracheal malformation and lung immaturity) when inactivated in mutant mice (3).

Reports on the effects of RA on surfactant...

...high levels of HFH-4 to the distal epithelium of transgenic mice results in the ectopic appearance of ciliated cells,  $\beta$ -tubulin IV mRNA, and \*suppression\* SP-B and SP-C signals (111). Also, transgenic lungs do not express the proximal marker CC10. It has been proposed that HFH-4 may... subsequently undergo lateral expansion (110). Invasion of the mesenchyme by the epithelial bud is mediated by epidermal growth factor (EGF) and TGF $\alpha$  signaling and is \*inhibited\* by TGF $\beta$ -1, presumably by stimulation of matrix synthesis and deposition at the epithelial-mesenchymal interface (27, 36). The transcription factor LEF1 (lymphoid enhancer binding...

...53). (A) Local expression of FGF-10 in the mesenchyme induces chemo-attraction and epithelial growth. (B) As the bud is induced, FGF-10 is \*inhibited\* by Shh expressed at the tips and by TGF $\beta$ -1 expressed throughout the subepithelial region. Concomitantly, proliferation is \*inhibited\* at the tips by FGF-10-mediated up-regulation of BMP-4. (C) These mechanisms limit bud outgrowth and expansion, resulting in cleft formation. FGF...

...synthesize RA, which diffuses and activates RA signaling ubiquitously (RAR/RXR in gray boxes represents activated RA signaling; RAR/RXR encircled in white boxes represents \*suppressed\* RA signaling). During branching, RA signaling is \*suppressed\* in the epithelium by P450RAI-mediated RA metabolism and by COUP-TFII \*inhibition\* of RAR/RXR activation of target genes (modified from 56).

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5/3,K/21 (Item 1 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

11342234 21417212 PMID: 11526082

**\*Suppression\* of head formation by Xmsx-1 through the \*inhibition\* of intracellular nodal signaling.**

Yamamoto T S; Takagi C; Hyodo A C; Ueno N  
Department of Developmental Biology, National Institute for Basic Biology, 38 Nishigonaka, Myodaiji, Okazaki, 444-8585, Japan.

Development (Cambridge, England) (England) Jul 2001, 128 (14)  
p2769-79, ISSN 0950-1991 Journal Code: 8701744

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

**\*Suppression\* of head formation by Xmsx-1 through the \*inhibition\* of intracellular nodal signaling.**

... the activation of several target genes encoding homeobox proteins, some of which are known to be necessary and sufficient for ventralization. Here, we used an \*inhibitory\* form of Xmsx-1, one of BMP's targets, to examine its role in head formation. Interestingly, ventral overexpression of a dominant Xmsx-1 \*inhibitor\* induced an ectopic head with eyes and a cement gland in the ventral side of the embryo, suggesting that Xmsx-1 is normally required to \*suppress\* head formation in the ventral side. Supporting this observation, we also found that wild-type Xmsx-1 \*suppresses\* head formation through the \*inhibition\* of nodal signaling, which is known to induce head organizer genes such as cerberus, Xhex and Xdkk-1. We propose that negative regulation of the BMP/Xmsx-1 signal is involved not only in neural induction but also in head induction and formation. We further suggest that the \*inhibition\* of nodal signaling by Xmsx-1 may occur intracellularly, through interaction with \*Smads\*, at the level of the transcriptional complex, which activates the activin responsive element.

Chemical Name: Bone Morphogenetic Proteins; DNA-Binding Proteins; FAST-1 protein; Homeodomain Proteins; \*Smad2\* protein; \*Smad4\* protein; Trans-Activators; Transcription Factors; \*hox\* 7.1 protein

5/3,K/22 (Item 1 from file: 370)  
DIALOG(R)File 370:Science

00508369 (USE 9 FOR FULLTEXT)

**The Taxonomy of Developmental Control in *Caenorhabditis elegans***

Ruvkun, Gary; Hobert, Oliver

The authors are in the Department of Molecular Biology, Massachusetts General Hospital, Department of Genetics, Harvard Medical School, Boston, MA 02114, USA.

Science Vol. 282 5396 pp. 2033

Publication Date: 12-11-1998 (981211) Publication Year: 1998

Document Type: Journal ISSN: 0036-8075

Language: English

Section Heading: Special Section

Word Count: 8026

(THIS IS THE FULLTEXT)

...Text: developmental genetics, and about 25% of the gene family has already been genetically analyzed. These genes mediate developmental processes ranging from spatial patterning by the \*Hox\* cluster subclass (B3) to neural differentiation and neurotransmitter specification by the unc-30 subclass (B7)...

...Seven of the *C. elegans* homeobox genes are probable orthologs of the *Drosophila* and vertebrate \*Hox\* cluster, corresponding roughly to one eve (vab-7), two AbdB (on YAC Y75B8), two Antp (egl-5 and mab-5), one Scr (lin-39), and...

...genes (B7) . Mutations in the four of these genes that have been studied genetically affect patterning along the anterior-posterior axis as precedent from *Drosophila* \*Hox\* cluster genetics would predict (B7) . The two AbdB class genes were previously missed in \*Hox\* cluster molecular and genetic analyses; these genes are closely related and located within 5 kb of each other, suggesting a recent gene duplication and possible redundancy. The *C. elegans* \*Hox\* genes are located on the same chromosome but are distributed over 3 Mb, with thousands of intervening genes, unlike the tandemly arranged clusters in *Drosophila* or vertebrates. The *C. elegans* \*Hox\* cluster is also missing particular genes that are present in both the *Drosophila* and vertebrate \*Hox\* clusters. The simplicity and partial dispersal of the *C. elegans* \*Hox\* cluster, as well as the phylogenetic placement of the Nematoda to the same phylogenetic lineage as arthropods suggest that its \*Hox\* cluster may be a derived, deleted version rather than a primitive ancestral \*Hox\* cluster. There is no detectable *C. elegans* Parahox cluster, although the caudal ortholog, which constitutes one member of the *Amphioxus* Parahox cluster, is located on the same chromosome as the disintegrating worm \*Hox\* cluster...

...The Polycomb (Pc) group of chromatin proteins have been implicated in \*repression\* of \*Hox\* cluster gene expression and heterochromatin formation in *Drosophila* and other animals (B10) . Many of the *Drosophila* Pc group that have mammalian orthologs are not present...chromatin remodeling proteins have been lost in the *C. elegans* evolutionary lineage. Those Pc group genes that remain may no longer function in maintenance of \*Hox\* gene expression. In contrast, there are clear *C. elegans* orthologs of the trithorax class genes ash1, ash2, Trx, and Brahma that have been implicated in establishment of \*Hox\* gene expression in *Drosophila* (B10)...

...Perhaps the partial dispersion of the *C. elegans* \*Hox\* cluster linkage and the loss of most Pc group genes are linked. For example, long range Pc class regulation of \*Hox\* gene chromatin structure may impose a genetic selection on the integrity of the \*Hox\* gene cluster that is so striking in the arthropod and chordate lineages. The relatively recent loss of this form of gene regulation in *C. elegans* may allow its \*Hox\* cluster to disperse. The presence of the *C. elegans* \*Hox\* genes on the same chromosome but not organized in tandem may represent a cluster in the process of disassembly after loss of the Pc genes...There are examples of enhancer function conserved across species, most notably between autoregulatory elements of the \*Hox\* gene cluster of arthropods and vertebrates (B19) .

Because of the precision with which expression patterns can be determined in *C. elegans* and correlated with the and three of these have been genetically analyzed. The genome sequence reveals two type I receptors, one type II receptor, and six \*Smad\* proteins that transduce signals from the receptors to the nucleus, and the functions of all of these genes have been genetically studied and ordered into...

...Of the six \*Smads\* revealed by the *C. elegans* genome sequence, three have been genetically implicated in DAF-7 signaling, and three others have been genetically implicated in DBL-1 signaling (B25) (B26) . The genomic ratios of three \*Smads\* per cognate receptor pair and the biochemical finding that mammalian \*Smad\* proteins form trimers upon receptor activation (B27) suggest that the three \*Smad\* proteins in each pathway form heterotrimers to propagate TGF- (beta) signals to downstream genes. Because these are the only TGF- (beta) receptor and \*Smad\* genes in the genome, the UNC-129 and other TGF- (beta) ligands are also likely to couple via these transduction pathways. The genome analysis leaves no room for other canonical TGF- (beta) receptors or \*Smads\*.

...diverse functions of these recently duplicated genes (B39) . All four ligands are likely to couple via these receptors, perhaps in distinct tissues. A *C. elegans* \*Suppressor\* of Hairless ortholog is likely to be the major transcriptional output of both receptors. Also detected in the genome sequence but not yet implicated in...genetic transformation of particular genetic regions, so that gene dosage can be increased in wild type or pathway mutants to search for high gene dosage \*suppression\* or enhancement of phenotypes. Gene fusions to the green fluorescent protein have been used extensively to reveal gene expression patterns and as molecular phenotypes with...is more phylogenetically general and thus primitive and which is derived in the comparisons of orthologs across phylogeny. Just as the universals and peculiarities of \*Hox\* gene function have been a major object of recent phylogenetic comparisons, we can expect many such orthologous pathways to be so analyzed...

...Caption:

Transcription factor genes.

Gene family	Genes identified		In <i>C. elegans</i>	Ortholog Not in <i>C. elegans</i>
	By sequence	Genetically		
Homeobox genes	83	24	51	11
*HOX* cluster	7	5	7	4
PAX	2	1	2	1
POU	3	3	1	0
LIM	7	6	6	0
Prd-type	14	4	9...signaling genes.	

Gene family	Genes identified	
	By sequence	Genetically
TGF- (beta) signaling pathway		
TGF- (beta) -like ligands	4	2
TGF- (beta) -like receptors	3	3
*Smad* proteins	6	6
Wg/Wnt signaling pathway		
Wnt-like ligands	5	3
Fz-like receptors	4	2
Signal transduction components:		
APC	1	1
dsh	3...	

References and Notes:

...T. Inoue and J. Thomas, personal communication; D. L. Riddle, personal communication. One other divergent \*Smad\*, bearing only one of the conserved domains of the gene family, is also present but has not been genetically studied...

5/3,K/23 (Item 1 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
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136100160 CA: 136(7)100160x JOURNAL  
**Molecular classification of human carcinomas by use of gene expression signatures**

AUTHOR(S): Su, Andrew I.; Welsh, John B.; Sapinoso, Lisa M.; Kern, Suzanne G.; Dimitrov, Petre; Lapp, Hilmar; Schultz, Peter G.; Powell, Steven M.; Moskaluk, Christopher A.; Frierson, Henry F., Jr.; Hampton, Garret M.

LOCATION: Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA

JOURNAL: Cancer Res. DATE: 2001 VOLUME: 61 NUMBER: 20 PAGES: 7388-7393 CODEN: CNREA8 ISSN: 0008-5472 LANGUAGE: English PUBLISHER: American Association for Cancer Research

5/3,K/24 (Item 2 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
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135103350 CA: 135(8)103350z PATENT  
**Genetic constructs containing stage-specific promoters and encoding blocker molecules for repressible sterility in animals**

INVENTOR(AUTHOR): Thresher, Ron; Hinds, Lyn; Hardy, Chris; Whyard, Steve; Vignarajan, Soma; Grewe, Peter Martin; Patil, Jawahar

LOCATION: Australia

ASSIGNEE: Commonwealth Scientific and Industrial Research Organisation

PATENT: PCT International ; WO 200148224 A1 DATE: 20010705

APPLICATION: WO 2000AU1596 (20001222) \*AU 994884 (19991224)

PAGES: 241 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-015/63A

DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CR; CU; CZ; DE; DK; DM; DZ; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; US; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

5/3,K/25 (Item 3 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
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134158510 CA: 134(12)158510m PATENT  
**The interaction of Smad6 with Hox proteins and BMB signalling and uses thereof in regulation of bone formation**

INVENTOR(AUTHOR): Cao, Xu; Shi, Xingming; Bai, Shuting

LOCATION: USA

ASSIGNEE: Uab Research Foundation

PATENT: PCT International ; WO 0111013 A2 DATE: 20010215

APPLICATION: WO 2000US40563 (20000803) \*US PV147161 (19990804)

PAGES: 34 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-000/A

DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

5/3,K/26 (Item 4 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)

**131295599 CA: 131(22)295599z PATENT**

**Inhibition of binding of Hox and homeodomain-containing proteins and a method for stimulating bone formation**

INVENTOR(AUTHOR): Cao, Xu; Shi, Xingming; Chang, Zhijie

LOCATION: USA

ASSIGNEE: The UAB Research Foundation

PATENT: PCT International ; WO 9951217 A1 DATE: 19991014

APPLICATION: WO 99US7455 (19990405) \*US 80859 (19980406)

PAGES: 79 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-031/00A; C07H-021/04B; C12Q-001/02B; C12Q-001/04B; C12Q-001/68B

DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SL; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

**5/3,K/27 (Item 1 from file: 266)**

DIALOG(R)File 266:FEDRIP

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00350497

IDENTIFYING NO.: 5R01NS38906-03 AGENCY CODE: CRISP

**NEURON DIFFERENTIATION IN C ELEGANS**

PRINCIPAL INVESTIGATOR: EMMONS, SCOTT W

ADDRESS: ALBERT EINSTEIN COLLEGE OF MED 1300 MORRIS PARK AVENUE BRONX, N Y 10461

PERFORMING ORG.: YESHIVA UNIVERSITY, NEW YORK, NEW YORK

SPONSORING ORG.: NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE  
FY : 2001

...SUMMARY: a bHLH transcription factor of the achaete/scute family. Differences among the rays are dependent on several transcription factors of the C. elegans \*Hox\* cluster, mab-5, egl-5, and Pax-6. The expression of these transcription factors may be regulated by extracellular factors. One extracellular factor t...

...DAF-4, type I and type II BMP receptors, respectively, and the products of the sma-2, sma-3, and sma-4, which are \*SMAD\* proteins. Among the differentiated characteristics of neurons is the expression of their complement of transmitters. Dr. Emmons proposes to focus on how neurotransmitter...

... processes: patterned expression of the ligand (DBL-1), pre-patterning of cell competence by egl-5 and some other unidentified gene, and lateral \*inhibition\*. The aims of this application are to: (1) examine the role of DBL-1, \*Hox\* genes, and other genes in inducing DA phenotype. TH::GFP expression will be examined in animals with mutations in BMP and \*Hox\* genes. This will determine whether all cells have equal competence to take on a DA phenotype, to distinguish between whether ray cells are prepatterned to respond to BMP or whether BMP is spatially patterned, and to determine whether \*Hox\* genes play a role in establishing competence to cells to respond to the BMP signal. It will also be determined whether there is an \*inhibitory\* pathway restricting DA expression. Animals with mutations in mab-21, which encodes a novel protein, will be examined for TH::GFP expression; wild-type...

**5/3,K/28 (Item 2 from file: 266)**

DIALOG(R)File 266:FEDRIP

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00319803

IDENTIFYING NO.: 1R01DK57501-01A1 AGENCY CODE: CRISP

**MECHANISM OF \*SMAD1\* MEDIATED OSTEOBLAST DIFFERENTIATION**

PRINCIPAL INVESTIGATOR: CAO, XU

ADDRESS: UNIV OF ALABAMA, BIRMINGHAM 1670 UNIVERSITY BLVD, VH G001  
BIRMINGHAM, AL 35294-0019

PERFORMING ORG.: UNIVERSITY OF ALABAMA AT BIRMINGHAM, BIRMINGHAM, ALABAMA

SPONSORING ORG.: NAT INST OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

FY : 2001

**MECHANISM OF \*SMAD1\* MEDIATED OSTEOBLAST DIFFERENTIATION**

...SUMMARY: superfamily, are potent growth factors in inducing osteoblast differentiation and stimulating bone formation. Signaling in TGF-beta superfamily is mediated by direct phosphorylation of \*Smad\* proteins. \*Smad2\* and \*Smad3\* are phosphorylated by TGF-beta and activin receptors, whereas phosphorylation of \*Smad1\* is specifically induced by bone morphogenetic proteins. Upon phosphorylation these \*Smad\* proteins interact with a common partner, \*Smad4\*, and translocate into the nucleus where the complex recruits DNA binding protein(s) to activate specific gene transcription. However, the DNA binding protein(s) involved in BMP signaling has not been identified. We have demonstrated that BMPs induce the interaction of \*Smad1\* with \*Hoxc-8\*, a member of the homeodomain transcription factor family. The interaction of \*Smad1\* with \*Hoxc-8\* inhibits the binding of \*Hoxc-8\* to its DNA binding site. \*Hoxc-8\* functions as a transcription repressor. A \*hox\* binding site is characterized from the 5'-flanking region of osteopontin gene, and BMP-induced osteopontin gene transcription is mediated through this \*Hox\* binding site. We hypothesize that BMP-2/4 induces osteoblast cell differentiation mediated by the \*Smad1\* interaction with \*Hoxc-8\*. The specific aims proposed are to: 1) characterize the specificity of the interaction between \*Smad1\* and \*Hox\* proteins in BMP2/4 signaling; 2) map domains that are responsible for the interaction between \*Smad1\* and \*Hoxc8\*. The effect of mapped \*Smad1\* interaction domains on gene transcription will also be assessed in luciferase reporter transfection studies. 3) Characterize the effects of the interaction between \*Smad1\* and \*Hoxc-8\* on osteoblast differentiation in human primary stromal cells. Further characterization of the interaction between \*Smad1\* and \*Hoxc-8\* will help us to understand the mechanism of BMP signaling and may yield a potential drug target to stimulate bone formation in osteoporosis...

DESCRIPTORS: biological signal transduction; cell differentiation; molecular site; connective tissue cell; reporter gene; genetic regulation; transcription factor; gene induction /\*repression\*; transforming growth factor; human tissue; immunoprecipitation; protein structure function; DNA binding protein; osteoblast; osteogenesis; osteopontin; yeast two hybrid system; bone morphogenetic protein; protein protein interaction

5/3,K/29 (Item 1 from file: 357)

DIALOG(R) File 357:Derwent Biotech Res.

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0268006 DBA Accession No.: 2001-07760 PATENT

**Regulating bone formation, useful e.g. for treating osteoporosis, comprises altering the activity of \*Smad6\* protein in forming complexes with \*Hoxc-8\* - \*Smad6\* protein and \*Hoxc-8\* protein interaction useful for drug screening**

AUTHOR: Cao X; Shi X; Bai S

CORPORATE SOURCE: Birmingham, AL, USA.

PATENT ASSIGNEE: Univ. Alabama 2001

PATENT NUMBER: WO 200111013 PATENT DATE: 20010215 WPI ACCESSION NO.:  
2001-191529 (2019)

PRIORITY APPLIC. NO.: US 147161 APPLIC. DATE: 19990804

NATIONAL APPLIC. NO.: WO 2000US40563 APPLIC. DATE: 20000803

LANGUAGE: English

**Regulating bone formation, useful e.g. for treating osteoporosis, comprises altering the activity of \*Smad6\* protein in forming complexes with \*Hoxc-8\* - \*Smad6\* protein and \*Hoxc-8\* protein interaction useful for**



**drug screening**

ABSTRACT: A method for regulating bone formation is claimed. It involves a composition (A) that alters the binding activity of \*Smad6\* protein, where an increase or decrease in \*Smad6\* increases or decreases \*Smad6\*/\*Hoxc\*-8 complexes and maintains or relieves transcriptional \*repression\* of genes involved in bone formation, respectively. Also claimed are: regulating nuclear bone morphogenetic protein (BMP) signaling in an animal; screening for compounds (I) that disrupt transcriptional \*repression\* of a gene; regulating expression of gene (II) that binds \*Hoxc\*-8 by altering the level of \*Smad6\* protein where \*Smad6\* may be increased by overexpression or upregulation of its gene, and decreased by antisense hybridization of \*Smad6\* RNA; and inducing transcription of a gene (III) that encodes osteopontin, osteoprotegrin, OPGL or RANK by \*inhibiting\* \*Smad6\*. The method is used e.g. to treat osteoporosis. The interaction between \*Smad6\* and \*Hoxc\*-8 is also used as the basis for screening assays to identify compounds that disrupt transcriptional regulation of gene, to regulate expression of genes that bind \*Hoxc\*-8, and for inducing transcription of the genes for osteopontin, osteoprotegrin, OPGL or RANK. (34pp)

DESCRIPTORS: recombinant Smad6, \*Hoxc\*-8 protein interaction, bone morphogenetic protein signal, antisense, antibody, appl. osteoporosis therapy, drug screening, gene expression regulation, gene transcription induction (Vol.20, No.15)

**5/3,K/30 (Item 2 from file: 357)**

DIALOG(R)File 357:Derwent Biotech Res.

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0246669 DBA Accession No.: 2000-01159 PATENT

**Stimulating bone formation, useful for preventing osteoporosis -  
interaction between a homeobox-containing transcriptional factor and an  
\*Smad1\* gene for cancer and cardiovascular disease regulation**

AUTHOR: Cao X; Shi X; Chang Z

CORPORATE SOURCE: Birmingham, AL, USA.

PATENT ASSIGNEE: UAB-Res.Found. 1999

PATENT NUMBER: WO 9951217 PATENT DATE: 19991014 WPI ACCESSION NO.:  
1999-610941 (1952)

PRIORITY APPLIC. NO.: US 80859 APPLIC. DATE: 19980406

NATIONAL APPLIC. NO.: WO 99US7455 APPLIC. DATE: 19990405

LANGUAGE: English

**- interaction between a homeobox-containing transcriptional factor and an  
\*Smad1\* gene for cancer and cardiovascular disease regulation**

ABSTRACT: A method for creating an interaction between a homeobox-containing transcriptional factor (hft) or \*Hox\* and (preferably) \*Smad1\* which removes transcriptional \*repression\* of the htf and allows induction of genes, is new. Also claimed are: a method for inducing genes which encode bone matrix proteins which involves the induction of an interaction between \*Smad1\* and a htf; a method for screening for a compound which stimulates bone formation which involves contacting a cell with a candidate compound and determining the ability of the compound to \*inhibit\* binding of the \*Hoxc\*-8 to a gene; and a method for regulating a disease which involves \*inhibiting\* the binding of hft to a disease-regulating gene, where \*inhibition\* of the binding removes transcriptional \*repression\* of the gene by the hft. The interaction between \*Smad1\* and \*Hoxc\*-8 is especially useful for inducing bone matrix proteins, especially osteopontin, which is useful for producing osteoblast and/or chondroblast differentiation. This may be useful...

DESCRIPTORS: bone formation stimulation method, homeobox-containing transcriptional factor, \*Smad1\*, appl. cancer, cardiovascular disease regulation, osteoporosis prevention DNA sequence protein sequence tumor (Vol.19, No.3)

**5/3,K/31 (Item 1 from file: 149)**

01976450 SUPPLIER NUMBER: 71185841 (USE FORMAT 7 OR 9 FOR FULL TEXT)

**Changes in the Expression of Transcription Factors in Pancreatic AR42J Cells During Differentiation Into Insulin-Producing Cells.**

Zhang, You-Qing; Mashima, Hiroshiro; Kojima, Itaru

Diabetes, 50, 2, S10

Feb,

2001

PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0012-1797

LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE: Professional

WORD COUNT: 3707 LINE COUNT: 00324

... s, annealing at 60 (degrees) C for 45 s, and extension at 72 (degrees) C for 45 s; and for *lmx1.2*, *lmx2*, *cdx4*, and *\*hox1\*.11*, denaturation at 94 (degrees) C for 1 min, annealing at 55 (degrees) C for 45 s, and extension at 72 (degrees) C for 45...into insulin-secreting cells. The mRNA for *Pax6*, *Nkx6.1*, and *Isl-1* was undetectable before and after differentiation. The mRNA for *lmx1.1*, *Pax4*, *\*Hox1\*.11*, and *neurogenin3* was upregulated during differentiation. Among them, the expression of *Pax4* and *neurogenin3* was markedly increased during differentiation (Fig. 1 and Table 2...

...1	276	-	-	+	+	
<i>cdx 2/3</i>	234	-	-	-	+	+
<i>cdx4</i>	194	+	+	+	+	+
<i>Nkx2.2</i>	187	+	+	+	+	+
<i>Nkx6.1</i>	280	-	-	-	+	+
<i>alx3</i>	170	-	-	-	-	+
<i>Pax4</i>	242	-	++	+	+	+
<i>Pax6</i>	545	-	-	-	+	+
<i>Pdx-1</i>	364	+	+	+	+	+
<i>HB9</i>	250	-	-	-	+	+
<i>*Hox1*.11</i>	366	-	+	-	-	+
<i>neurogenin3</i>	222	-	++	-	-	+
<i>Beta-2</i>	400	+	+	+	+	+

AR42J cells were incubated for 72 h with 2 nmol/l activin A and 100 pmol/l HGF...

...not reproduce the effect of activin A--namely morphological changes and the expression of PR It was shown recently that *Pax4* functions as a transcription \*repressor\* (19,20). It binds to the potential binding sites for *Pax6* and blocks the *Pax6*-induced activity. As shown in Fig. 1, *Pax6* is not...promoter augmented the formation of pancreatic endocrine cells in transgenic mice. They postulated that formation of endocrine cells from their progenitors is regulated by "lateral \*inhibition\*" involving the Notch signaling system. Our results indicate that the expression of *neurogenin3* is also regulated by activin A. Because activin A does not alter...

...activin A (21). Miralles et al. (22). showed that conversion of progenitor cells to endocrine or exocrine cells is modulated by mesenchyme-derived follistatin, an \*inhibitor\* of activin A (23). Given that activin A is involved in the differentiation of pancreatic endocrine cells (24,25), these results imply that differentiation of...

...AR42J cells by hepatocyte growth factor. Endocrinology 137:3969-3976, 1996

(16.) Zhang Y-Q, Kanzaki M, Furukawa M, Ozeki M, Kojima I: Involvement of \*Smad\* proteins in the differentiations of pancreatic AR42J cells induced ...U S A 97:1607-1611, 2000

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(20.) Fujitani Y, Kajimoto Y, Yasuda T, Matsuoka T, Kaneto H, Umayahara Y, Fujita N, Watada H, Miyazaki J, Yamasaki Y, Hori M: Identification of a portable \*repression\* domain and an EIA-responsive

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